CHEMOENZYMATIC SYNTHESIS AND UTILITY OF VINYL AZIRIDINES: AN APPROACH TO THE SYNTHESIS OF (+)-7-DEOXYPANCRATISTATIN AND THE PREPARATION OF SEVERAL TRUNCATED ANALOGS

By

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In memory of my mother.

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Approaches to the syntheses of (+)-7-deoxypancratistatin (**6**) as well as several structurally related truncated analogs (**296**) are described by chemical manipulation of the enantiomerically pure bromocyclohexadiene-*cis*-diol (**1b**). Among the key steps in the synthesis of the truncated analogs are the S_N2 opening of a vinylaziridine (**298**) which gives a functionalized cyclohexene (**297**) and oxidative degradation of the cyclohexene (**297**) to give the desired derivatives (**296**). The approach to the synthesis of (+)-7-deoxypancratistatin (**6**) is based on the selective opening of the oxirane in an epoxyaziridine (**301**) by piperonylic species. Unfortunately, selective opening of the aziridine ring was found to occur resulting in formation of the functionalized epoxide (**329**), only ascertained through the identification of the tetraacetate (**353**) at the end of the synthesis which was aided by ^{15}N spectroscopy. Lewis acid mediated intramolecular cyclization of the epoxide (**329**) gave the corresponding alcohol (**332a**) which was

ultimately transformed into the final tetracetate (**353**). A corrected approach to the synthesis of (+)-7-deoxypancratistatin (**6**) will be described in which the selective opening of a cyclic sulfate (**360**) by nucleophilic species serves as the key step.

CHAPTER 1
INTRODUCTION

Aziridines are useful synthetic intermediates as evidenced by the extensive reviews[1] on the chemistry of aziridines and their utility in the synthesis of biologically important compounds.[2] Over the last decade, chiral aziridines have emerged as an attractive class of compounds for asymmetric synthesis since a number of procedures are available for the preparation of these heterocycles in enantiomerically pure (or highly enriched) form. As a result of the intrinsic ring strain and polarization, aziridines are rendered susceptible to ring-opening reactions which dominate their chemistry. Moreover, such reactions often proceed in a highly stereospecific and regioselective manner, chemoselectivity dictated by the nature of substituents on the carbon and nitrogen atoms, which makes aziridines useful substrates for synthetic endeavors.

Among the variously functionalized aziridines, vinylaziridines have proven to be the most interesting and useful compounds as a consequence of the unique transformations[3] and rearrangements[4] which vinylaziridines undergo. Nevertheless, methodologies for the preparation of these molecules are few in number and are usually plagued by low overall yields. The utility of vinyl aziridines stems from the presence of two reactive sites, the three-membered ring and the olefin, each of which possesses distinct chemical reactivity and thus can be independently functionalized.

Halocyclohexadiene-*cis*–diols **1a-b** have served not only as precursors to optically pure vinylaziridines[5] but also as chiral synthons in the enantioselective

syntheses of several natural products, including manojirimycin (**2**),[6] (+)-kifunensine (**3**),[7] specionin (**4**),[8] and (+)-lycoricidine (**5**)[9] among others. The diols **1a-b** contain elements useful for both diastereoselective and regioselective chemical operations; that is, diastereoselectivity is controlled through steric effects associated with the diol moiety, while regioselectivity is governed by the polarization of the diene system. These chemical features must be considered during the course of designing the enantioselective synthesis of target molecules.

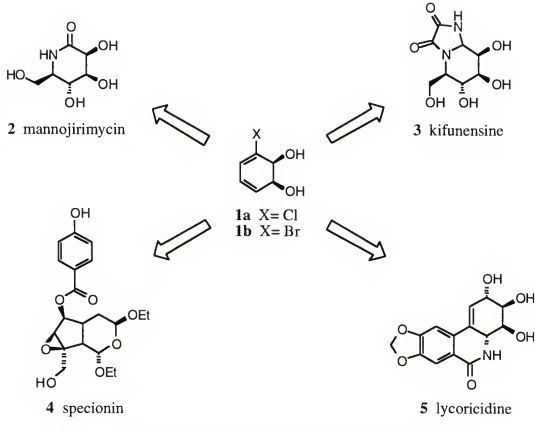
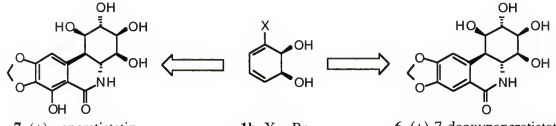


Figure 1. Alkaloids Derived from Halocyclohexadiene-*cis*–diols.

In order to demonstrate the utility of the diols **1a-b** in organic chemistry, approaches to the total syntheses of (+)-7-deoxypancratistatin (**6**) in addition to several

structurally related truncated analogs will be described. The regioselective and stereospecific chemical operations used in attempting to correctly set the six contiguous chiral centers of the C ring in the alkaloid will be discussed. This methodology will ultimately serve as a model for the synthesis of the more potent alkaloid, (+)-pancratistatin (**7**), and thus sustains the creditability of halocyclohexadiene-*cis*–diols **1a-b** in rational synthetic design.



7 (+)-pancratistatin **1b** X = Br **6** (+)-7-deoxypancratistatin

Figure 2. *Amaryllidaceae* Alkaloids Derived from Bromocyclohexadiene-*cis*-diol

CHAPTER 2
HISTORICAL

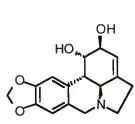
Amaryllidaceae Alkaloids

Isolation and Structure Determination

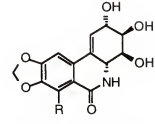
The use of plant extracts derived from the *Amaryllidaceae* family for medicinal purposes dates back to at least the fourth century;[10] moreover, several alkaloids possessing a diverse array of biological activities have been isolated from this species in more recent times. The *Amaryllidaceae* alkaloids constitute a class of natural products consisting of over 1000 species in 85 distinct genera.[11] Over thirty different plants of the *Amaryllidaceae* family are in use today as agents in the primitive treatment of cancer. In 1877, the first member of the *Amaryllidaceae* species, lycorine (**8**), was isolated from *Narcissus pseudonarcissus.*[12] During the late 1960s, the Okamoto research group discovered the presence of narciclasine (**9**) as well as lycoricidine (**5**) in *Lycoris radiata.*[13] In the past two decades, Pettit and co-workers extracted a more highly oxygenated phenanthridone alkaloid, pancratistatin (**7**), from *Pancratium littorale,*[14] while the laboratories of Ghosal[15] reported the isolation of 7-deoxpancratistatin (**6**) from the bulbs of *Haemanthas kalbreyeri.* In addition to these natural products, more than 100 unique tyramine based structures have been found in the *Amaryllidaceae* family since the initial disclosure of the alkaloidal constituents present within this species of plant.

Biological Activity

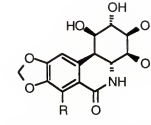
Many of the natural products derived from the *Amaryllidaceae* family display a wide spectrum of pharmacological properties, most notably the confirmed levels of



8, lycorine



5, R = H, lycoricidine
9, R = OH, narciclasine



6, R = H, 7-deoxypancratistatin
7, R = OH, pancratistatin

Figure 3. Representative *Amaryllidaceae* Alkaloids

anticancer activity exhibited by certain alkaloids within this class. The work of the Fitzgerald group[16] in 1958 has demonstrated that the antitumor activity of lycorine stems from its ability to inhibit murine P-388 lymphocytic leukemia. Both narciclasine and lycoricidine inhibit the growth of murine Ehrlich carcinoma and also exhibit carcinostatic activity.[13, 17] Narciclasine displays anticancer activity against human HeLa and HEP_{II} carcinomas,[13, 18] while pancratistatin has shown antitumor activity *in vivo* against murine P-5076 ovarian sarcoma in addition to murine P-388 lymphocytic leukemia.[19] Furthermore, clinical studies have suggested that pancratistatin exhibits notably higher therapeutic indices relative to its congeners narciclasine and lycoricidine. The antineoplastic activity of pancratistatin has also been detected within 7-deoxypancratistatin *in vitro*; moreover, a better therapeutic index has been observed for 7-deoxypancratistatin relative to pancratistatin as a result of decreased toxicity.[20]

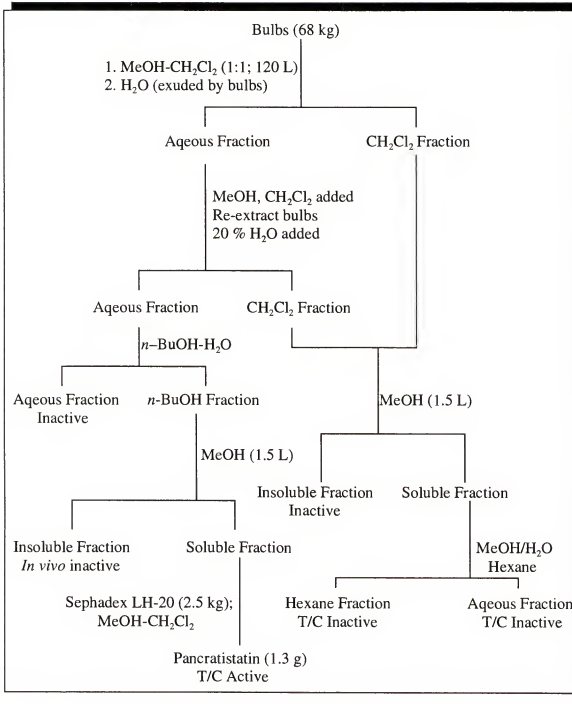


Figure 4. Isolation of Pancratistatin

Of these alkaloids, only the mode of action by which narciclasine exhibits its antineoplastic activity is well documented.[21] Studies have established that the mechanism of action for narciclasine involves inhibition of the growth of eukaryotic cells via obstruction of protein biosynthesis. Specifically, results suggest that narciclasine prevents binding of tRNA to the peptidal transferase center of the 60s ribosomal subunit.[21a] As a result of the structural similarities among narciclasine, pancratistatin, and 7-deoxypancratistatin, it has been speculated that similar modes of activity exist for all of these alkaloids; nevertheless, a more detailed explanation for pancratistatin's and 7-deoxypancratistatin's mechanism of action has not presently been elucidated.

Total Syntheses

The portfolio of biological activity displayed by certain members of the *Amaryllidaceae* family as well as the challenging structural motifs found in these alkaloids, which are exemplified by narciclasine (**9**), lycoricidine (**5**), pancratistatin (**7**) and 7-deoxypancratistatin (**6**), has prompted the synthetic community to prepare several of these natural products.[22] The synthesis of lycoricidine[9, 23] has been reported by several groups; in addition, the unnatural enantiomer (-)-lycoricidine has also been successfully prepared.[24] More recently, the asymmetric synthesis of the natural enantioner (+)-narciclasine[25,27e] has been reported by two research groups. Since the initial racemic synthesis of (+/-)-pancratistatin by Danishefsky and Lee[26] in 1989, there have been four total asymmetric syntheses of (+)-pancratistatin[27] as well as one formal synthesis of the alkaloid.[28] The natural product (+)-7-deoxypancratistatin has also been synthesized several times,[29] including two syntheses[23a-b] in route to lycoricidine which were performed prior to the isolation of (+)-7-deoxypancratistatin from natural resources. The following

section will discuss the methodology employed in the total syntheses of (+)-pancratistatin (**7**) and (+)-7-deoxypancratistatin (**6**) and will describe various synthetic approaches to the preparation of these natural products.

The most notable structural features which complicate synthetic endeavors aimed at preparing these alkaloids include the *trans* B-C amide ring junction, the high degree of substitution of the aromatic A-ring, and the stereochemistry pertaining to the various functionalities embedded along the C-ring. In general, the majority of the syntheses initially construct the A- and C-rings and then establish the B-C ring junction which results in formation of the phenanthridone core present in these alkaloids.[22]

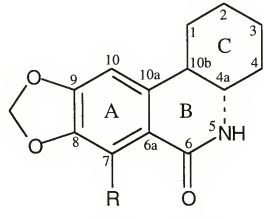


Figure 5. Phenanthridone System

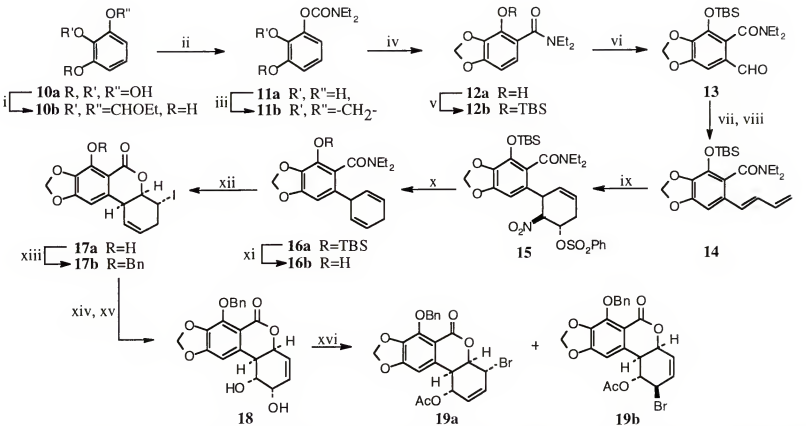
Pancratistatin

As shown in Scheme 1, the first total synthesis of (+/-)-pancratistatin disclosed by Danishefsky and Lee[26] began with pyrogallol **10a** which was converted to orthoester **10b** using triethyl orthoformate. Carbamoylation of phenol **10b** with diethylcarbamoyl chloride, cleavage of the orthoester, and construction of the methylenedioxy unit afforded

11b which was transformed into amide **12a** in modest yield via an anionic Fries rearrangement. Protection of the hydroxyl group as the silyl ether followed by *ortho*-lithiation and subsequent treatment with N,N-dimethylformamide generated aldehyde **13**. Formation of the arylbutadiene **14** was achieved by treatment of aldehyde **13** with allylmagnesium bromide, activation of the resulting alcohol with mesyl chloride, and elimination of the homoallylic mesylate with DBU. A Diels-Alder reaction of diene **14** with β-nitrovinylsulfone gave cyclohexene **15** which was reduced with tri-*n*-butyltin hydride to furnish cyclohexadiene **16a**. Deprotection of silyl ether **16a** with tetra-*n*-butylammonium flouride followed by treatment of the resulting alcohol with bis(tributyltin)oxide furnished the corresponding stannyl ether which upon exposure to iodine afforded lactone **17a**. Benzylation of the phenol followed by catalytic osmylation produced the corresponding diol lactone which, upon treatment with DBU, underwent an elimination to form diol **18**. In a Moffatt-like transformation, diol **18** was treated with 2-acetoxyisobutyl bromide to provide the acetoxy derivatives **19a** and **19b**. Dihydroxylation of the olefin in **19b** furnished diol **20**, an intermediate containing a fully functionalized C-ring present in pancratistatin. Following an intricate protection and reductive elimination sequence, imidate **23** was prepared from alcohol **22** by reaction with sodium hydride and trichloroacetonitrile. Pyrolysis of imidate **23** invoked an Overman rearrangement to generate trichloroacetamide **24** which was converted into diol **25** by catalytic osmylation. Treatment of diol **25** with potassium carbonate in refluxing methanol resulted in successful hydrolysis of the lactone to produce lactam **26** after DCC coupling of the intermediate amino acid. Removal of the benzyl group provided the target molecule (+/-)-pancratistatin in 26 steps and in an overall 0.13 % yield.

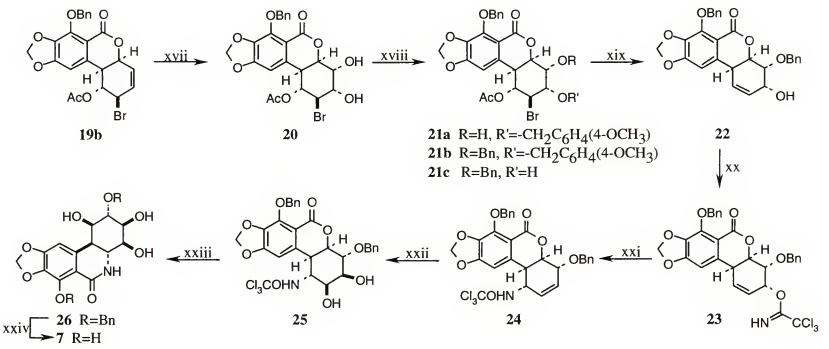
The first asymmetric synthesis of (+)-pancratistatin was published by Hudlicky and co-workers[27a,b] in 1995 as illustrated in Scheme 2 which started from the enatiomerically pure synthon **1b** obtained by whole cell bio-oxidation of bromobenzene.[30] Protection of the diol as the acetonide under standard conditions followed by reaction with (N-tosylimino)phenyliodinane[31] according to Evans' protocol[32] furnished vinylaziridine **27** which was subsequently reduced to aziridine **28** under radical conditions. In the pivotal step of the synthesis, stereospecific opening of aziridine **28** with a higher order cyanocuprate ($Ar_2Cu(CN)_2Li$) in a S_N2 fashion gave rise to tosylamide **29** which contains the carbocyclic skeleton of the natural product. Conversion of primary tosylamide **29** into the N-acyl derivative **30** and subsequent reductive detosylation afforded carbamate **31** following desilylation. Reduction of the aryl amide moiety and protection of the phenol as the benzyl ether produced aldehyde **32** which was oxidized to acid **33** and immediately converted into methyl ester **34**. Following deprotection of the acetonide, hydroxyl directed epoxidation generated epoxide **35** stereospecifically as the cyclization precursor. Treatment of epoxide **35** with a catalytic amount of sodium benzoate resulted in deprotection of the carbamate, ensuing cyclization to the lactam, solvolysis of the epoxide and debenzylation to ultimately furnish (+)-pancratistatin in an overall yield of 2 % and in 13 steps.

An additional enantioselective synthesis of (+)-pancratistatin depicted in Scheme 3 was achieved by Trost and Pulley[27c] which took advantage of the availablity of diol **36** and its palladium-catalyzed desymmetrization.[33] After protection of the diol as the dicarbonate, desymmetrization in the presence of a chiral ligand afforded azide **37** in greater than 95 % enantiomeric excess. Treatment azide **37** with cuprous cyanide and



i. $HC(OEt)_3$, Amberlyst-15, benzene; ii. NaH, THF, Et_2NCOCl, DMAP; iii. K_2CO_3, CH_2Br_2, CuO, DMF; iv. a) *s*-BuLi, TMEDA, THF; b) NH_4Cl; v. TBSCl, imidazole, CH_2Cl_2; vi. a) *s*–BuLi, TMEDA, THF; b) DMF; vii. Allylmagnesium bromide, Et_2O; viii. a) CH_3SO_2Cl; Et_3N, CH_2Cl; b) DBU; ix. 1-(benzenesulfonyl)-2-nitroethene, $CHCl_3$; x. Bu_3SnH, AIBN, toluene; xi. TBAF, THF; xii. a) $(Bu_3Sn)_2O$, toluene; b) I_2; THF; xiii. BnBr, Ag_2O, DMF; xiv. OsO_4, NMO, CH_2Cl_2, THF, H_2O; xv. DBU, benzene; xvi. 2-acetoxyisobutyryl bromide, CH_3CN.

Scheme 1. First Total Synthesis of (+/-)-Pancratistatin (Part I)



xvii. OsO_4, NMO, CH_2Cl_2, THF, H_2O; xviii. a) Bu_2SnO, toluene; then 4-methoxybenzyl bromide, *n*–Bu_4NI; b) BnBr, Ag_2O, DMF; c) DDQ, CH_2Cl_2, H_2O; xix. Zn(dust), AcOH, H_2O, CH_2Cl_2; xx. NaH, CCl_3CN, THF; xxi. 100-105 °C, 0.05-0.1 mmHg; xxii. OsO_4, NMO, THF, H_2O; xxiii. K_2CO_3, MeOH, CH_2Cl_2; then DCC, CH_2Cl_2; xxiv. H_2, $Pd(OH)_2$, EtOAc.

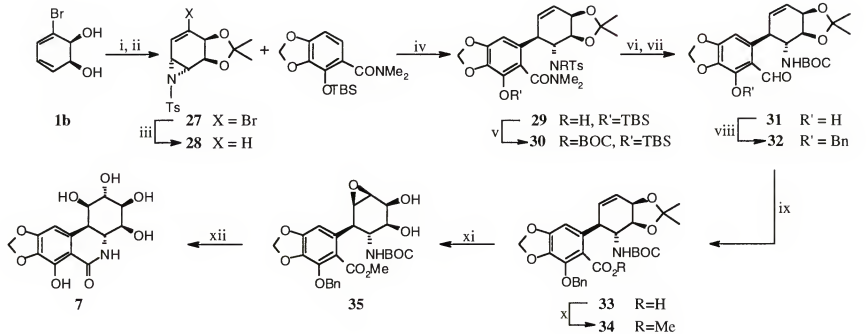
Scheme 1. First Total Synthesis of (+/-)-Pancratistatin (Part II)

aryl Grignard reagent resulted in a S_N2' addition to form azide **38** which contains a cyclohexene unit resembling the C-ring of the alkaloid. Dihydroxylation of the olefin, protection of the resulting hydroxyl groups, and bromination of aromatic ring generated aryl bromide **39** as the precursor to cyclization. Conversion of azide **39** to the corresponding isocyanate was followed by metal halogen exchange to give an aryllithium species which underwent cyclization producing lactam **40**, an intermediate which contains the core of the natural product. Desilylation of lactam **40** gave the the resulting diol which was converted into cyclic sulfate **41**. Stereospecific and regioselective nucleophilic attack of sulfate **41** with cesium benzoate gave rise to ester **42** following simultaneous clevage of the acetonide and the alkyl sulfate under acidic conditions. Removal of the benzoyl and methyl ether groups completed the synthesis of (+)-pancratistatin in 15 steps from diol **36** and in an 11 % overall yield.

A formal synthesis of (+)-pancratistatin was disclosed by the Haseltine group[28] in 1997 as displayed in Scheme 4 which intercepted a late stage intermediate of Danishefsky and Lee's[26] synthesis. The synthesis began with diol **36** which was subjected to the sequence for desymmetrization of Johnson et al.:[34] enzymatic acetylation to furnish acetate **43a**, protection to give silyl ether **43b** and deacetylation to afford alcohol **43c**. Benzylation of the alkoxide derived from alcohol **43c** with piperonyl bromide generated allylic alcohol **44** after removing the silyl group. The carbon skeleton was obtained via an intramolecular cyclization of piperonylated conduritol **44** to produce pentacycle **45** which was oxidized to acetal **46a** as a single diastereomer. The installed acetal tether in **46a** was used to direct lithiation of the arene ring which gave phenol **46b** upon oxidation. Deprotection of the acetal group in phenol **46b** gave the corresponding

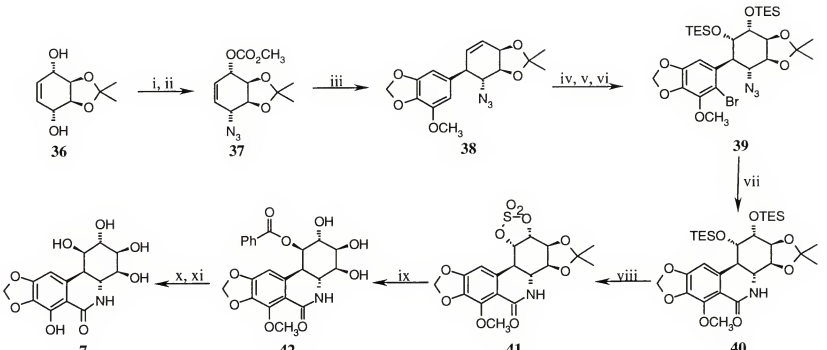
lactol **47** which upon oxidation and ketal hydrolysis furnished lactone **48**. Selective protection of the allylic hydroxyl group in lactone **48**, benzylation of the remaining alcohol, and hydrolysis of the methoxyethoxymethyl ether afforded alcohol **49c** whose spectral data were consistent with those reported by Danishefsky and Lee,[26] thus establishing a formal synthesis of (+)-pancratistatin.

As shown in Scheme 5, Magnus and Sebhat[27d] are credited with a total synthesis of (+)-pancratistatin which starts with addition of the aryllithium species derived from 3,4-methylenedioxy-5-methoxybromobenzene to ketone **50** producing the styrene derivative **51** after dehydration. Catalytic hydrogenation of the olefin followed by ketal hydrolysis afforded cyclohexanone **52** which was converted to triisopropylsilyl enol ether **53** in greater than 85 % enantiomeric excess. Treatment of silyl enol ether **53** with iodosylbenzene resulted in a β-azidonation reaction furnishing azide **54** as a mixture (3.5:1) of *trans*- and *cis*- diastereomers. Reduction of the azide functionality and subsequent protection of the corresponding amine generated carbamate **55**. Treatment of carbamate **55** with *m*-chloroperoxybenzoic acid followed by acid catalyzed hydrolysis of the resulting silyl enol ether gave ester **56a** stereoselectively. Epimerization of carbamate **56a** under basic conditions (*t*-BuOK, HMPA) gave the more stable equatorial isomer **56b** which was subsequently converted into silyl enol ether **57**. Transformation of enol ether **57** to enone **58** was accomplished through a two sequence involving selenylation followed by oxidative elimination. Stereoselective epoxidation of enone **58** followed by reduction of the ketone functionality gave rise to carbamate **59**. Treatment of epoxide **59** with sodium benzoate in water under solvolytic conditions followed by acetylation of the resulting tetraol afforded polyacetate **60** which upon Bischler-Napieralski cyclization



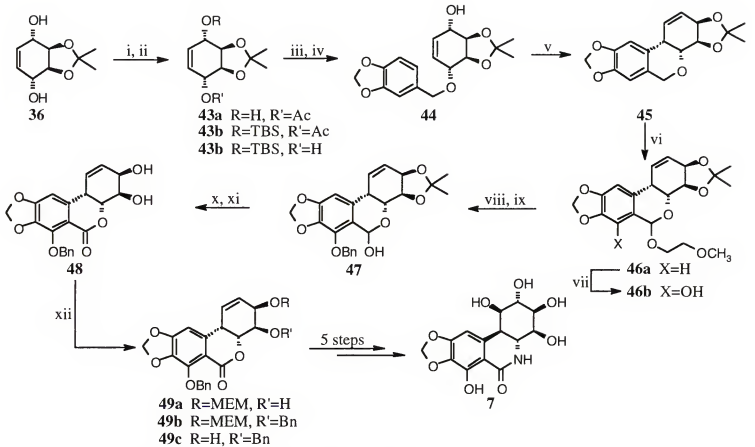
i. DMP, *p*–TsOH, acetone; ii. PhI=NTs, $Cu(acac)_2$, CH_3CN; iii. Bu_3SnH, AIBN, THF; iv. a) *s*–BuLi, TMEDA, THF; b) aziridine **28**; c) BF_3Et_2O; v. *s*–BuLi, $(BOC)_2O$, THF; vi. Na/anthracene, DME; vii. Morpholine-SMEAH, THF; viii. BnBr, K_2CO_3, DMF; ix. $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*–BuOH, H_2O; x. CH_2N_2; xi. a) HOAc, THF, H_2O; b) *t*-BuOOH, $VO(acac)_2$, benzene; xii. C_6H_5COONa, H_2O, 100 °C.

Scheme 2. First Asymmetric Synthesis of (+)-Pancratistatin.



i. *n*–BuLi, THF; then methyl chloroformate; ii. 0.5 mol % $(\pi\text{-}C_3H_7PdCl)_2$. 0.75 mol % chiral ligand, $TMSN_3$, CH_2Cl_2; iii. 1,2-(methylenedioxy)-3-methoxybenzenemagnesium bromide, CuCN, THF, ether; iv. cat. OsO_4, $NMOH_2O$, CH_2Cl_2; v. $TESOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2; vi. NBS, DMF; vii. a) $(CH_3)_3P$, THF, H_2O; b) $COCl_2$, THF, $(C_2H_5)_3N$; c) *t*–BuLi, ether, -78 °C; viii. a) TBAF, THF, -78 °C to 0 °C; b) $SOCl_2$; $(C_2H_5)N$; c) cat. $RuCl_3H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O; ix. $PhCO_2Cs$, DMF; then workup with THF, H_2O, cat. H_2SO_4; x. K_2CO_3, CH_3OH; xi. LiCl, DMF.

Scheme 3. Total Asymmetric Synthesis of (+)-Pancratistatin



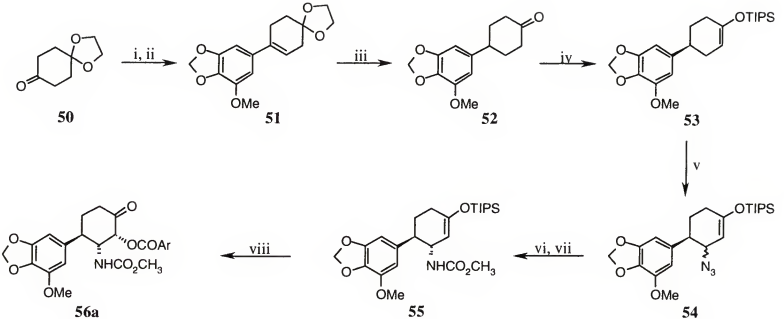
i. Amano P-30 lipase, isoprenyl acetate, ii. a) TBSCl, imidazole, DMF; b) K_2CO_3, MeOH; iii. NaH, piperonyl bromide, Bu_4NI, THF; iv. TBAF, THF; v. Tf_2O, 2,6-lutidine, CH_2Cl_2; vi. DDQ, 2-methoxyethanol, CH_2Cl_2; vii. *t*–BuLi, DME; then $B(OCH_3)_3$; then $HOAc/H_2O_2$; viii. NaH, BnBr, Bu_4NI, THF; ix. CSA, THF, H_2O; x. TPAP, NMO, CH_2Cl_2; xi. HCl, H_2O, THF; xii. a) MEMCl, iPr_2NEt, CH_2Cl_2; b) Ag_2O, BnBr; c) *p*–TsOH, MeOH.

Scheme 4. Formal Synthesis of (+)-Pancratistatin

followed by deprotection of the acetate groups furnished (+)-pancratistatin in 22 steps and in 1.2 % overall yield.

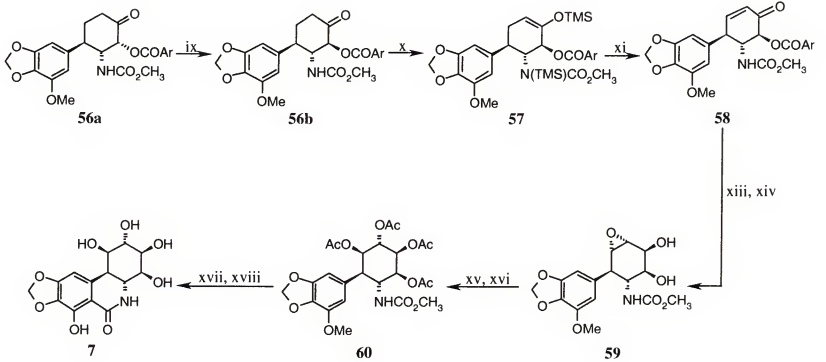
Most recently, Rigby and co-workers[27e] have synthesized (+)-pancratistatin in which a stereo- and regiocontrolled aryl enamide photocyclization serves to construct the *trans*-fused phenanthridone system present in the alkaloid as illustrated in Scheme 6. The enantiomerically pure *syn*-epoxy alcohol **61**, obtained through McGowen and Berchtold's procedure,[35] was protected as its silyl ether and subsequently hydrolyzed to provide acid **62**. After conversion of acid **62** to the isocyanate **63** via a Curtius rearrangement, addition of the lithiated species derived from aryl bromide **64** resulted in formation of enamide **65** as the cyclization precursor. Irradiation of enamide **65** under standard conditions gave rise to the phenanthridone **66** which contains the correct stereochemistry present in the core structure of (+)-pancratistatin. Alkylation of the phenol, removal of the silyl protecting group, oxidation of the ensuing alcohol, and stereoselective reduction of the resulting ketone furnished epoxide **68** after benzylation. Selective axial opening of epoxide **68** with a phenylselenide species followed by selenoxide elimination afforded allylic alcohol **69** which was subsequently dihydroxylated to provide the triol **70** in good yield. Simultaneous removal of both the benzyl and *p*-methoxybenzyl protecting groups via hydrogenolysis followed by removal of the methyl group furnished (+)-pancratistatin in 17 steps and in 2.8 % overall yield from epoxy alcohol **61**.

The structural intricacy of (+)-pancratistatin has posed a challenge to the synthetic community thus resulting in only six syntheses of the alkaloid. Both the control of stereochemistry of the functionalities along the C-ring and the establishment of the *trans* B-C ring junction become a formidable task for any synthetic endeavor aimed at



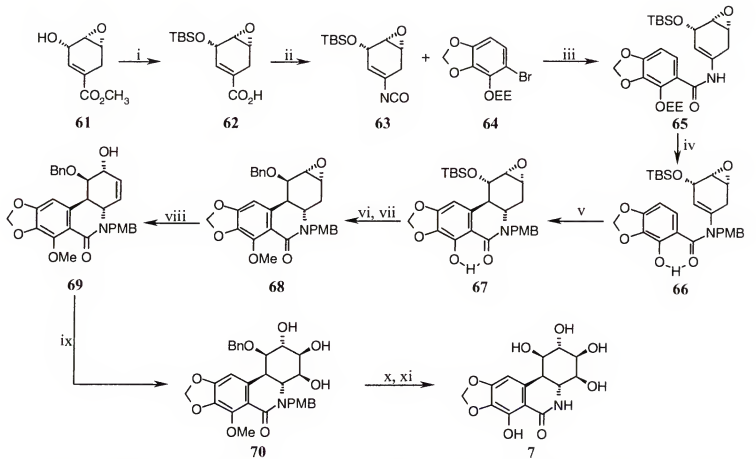
i. 3,4-methylenedioxy-5-methoxybromobenzene, *n*–BuLi, THF, -78 °C; ii. DBU, $POCl_3$ pyridine; iii. a) H_2, Pd/C, MeOH; b) H_2SO_4, H_2O, dioxane; iv. (+)-bis(α-methylbenzyl)amine, *n*–BuLi, THF, -78 °C, then LiCl, TIPSOTf, THF; v. PhIO, $TMSN_3$, CH_2Cl_2,; vi. $LiAlH_4$, Et_2O; vii. CH_3OCOCl, pyridine, CH_2Cl_2; viii. a) *m*CPBA, imidazole, CH_2Cl_2; b) EtOH, HCl, H_2O.

Scheme 5. Total Synthesis of (+)-Pancratistatin (Part I)



ix. *t*–BuOK, HMPA; x. Et_3N, TMSOTf, CH_2Cl_2; xi. $AgCO_2CF_3$, PhSeCl, CH_2Cl_2; then H_2O_2, pyridine, CH_2Cl_2; xiii. $NaHCO_3$, H_2O_2, THF, MeOH, H_2O; xiv. L-selectride, THF; xv. $C_6H_5CO_2Na$, H_2O, 100 °C; xvi. Ac_2O, pyridine; xvii. Tf_2O, DMAP, CH_2Cl_2; xviii. a) BBr_3, CH_2Cl_2, -78 °C; b) NaOME, THF.

Scheme 5. Total Synthesis of (+)-Pancratistatin (Part II)



i. a) TBSCl, imidazole; b) LiOH; ii. a) DPPA; b) toluene, 110 °C; iii. *n*-BuLi, THF; iv. a) NaH, *p*-methoxybenzylbromide; b) PPTS; v. hv, benzene; vi. a) NaH, MeI; b) TBAF; vii. a) Dess-Martin, CH_2Cl_2; d) $NaBH_4$; b) NaH, BnBr; viii. $(PhSe)_2$, $NaBH_4$, H_2O_2; ix. OsO_4; *t*-BuOH; x. H_2, $Pd(OH)_2$; xi. LiCl, DMF.

Scheme 6. Total Synthesis of (+)-Pancratistatin

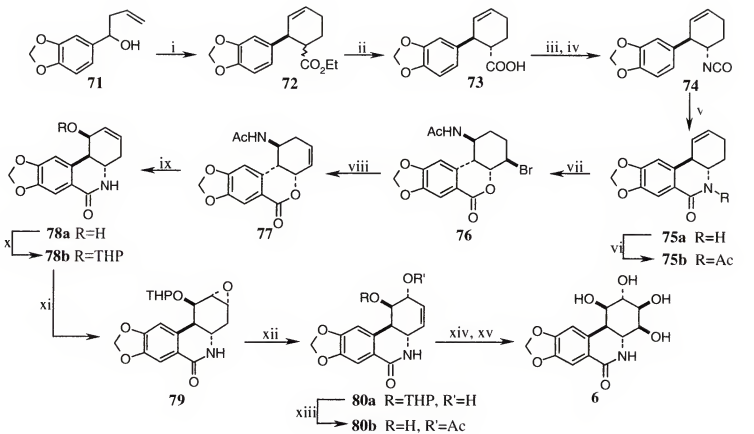
preparing the natural product in enantiopure form. The development of more efficient methodology towards constructing the six contiguous asymmetric centers will lead to a more practical synthesis of the alkaloid, and research in this area remains to be performed in the future.

7-Deoxypancratistatin

The earliest synthesis of 7-deoxypancratistatin dates back to 1976 when Ohta and Kimoto[23a] prepared the alkaloid in racemic form, prior to its isolation from natural resources, in route to the prepration of (+/-)-lycoricidine. Reaction of ethyl acrylate with 3,4-methylenedioxyphenyl allyl carbinol **71** furnished a mixture of Diels-Alder adducts **72** which were used to prepare acid **73** as displayed in Scheme 7. Acid **73** was converted into the corresponding acyl azide via a modified Curtius reaction which was used to generate isocyanate **74** as the cyclization precursor. Lewis acid catalysis led to successful formation of lactam **75a** which was protected as its acetate. Hydrolysis of lactam **75b**, bromination of the resulting olefinic acid, and subsequent lactonization generated the acetamide **76**. Base induced elimination of acetamide **76** provided olefin **77** which underwent transamidation upon exposure to aqeous sodium hydroxide producing alcohol **78a**. Protection of alcohol **78a** as its tetrahydropyranyl ether followed by oxidation of the olefinic bond gave epoxide **79** which was transformed into allylic alcohol **80a** using Sharpless and Lauer's procedure.[36] Acetylation of the hydroxyl functionality, removal of the tetrahydropyranyl protecting group, stereocontrolled dihydroxylation of the olefin, and hydrolysis of the acetate afforded the alkaloid in racemic form, which was used to prepare (+/-)-lycoricidine via a dehydration protocol.

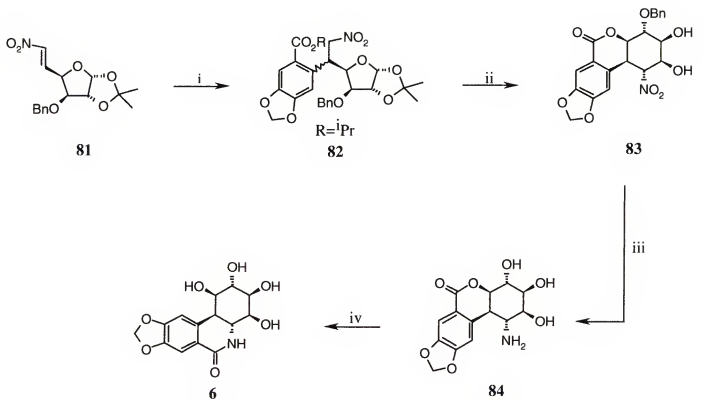
The first asymmetric preparation of (+)-7-deoxypancratistatin was performed by Paulsen and Stubbe[23b] in route to (+)-lycoricidine in which the chirality is derived from D-glucose as illustrated in Scheme 8. Reaction of the aryl anion derived from isopropyl 6-bromo-(3,4-methylenedioxy)benzoate with olefin **81** gave rise to acetonide **82** as a mixture of idofuranose and glucofuranose derivatives. Cleavage of the acetonide in the mixture of furanose derivatives with acetic acid followed by cyclization of the resulting diol under basic conditions (K_2CO_3, MeOH) afforded lactone **83** which contains the functionalized C-ring of the alkaloid. Reduction of the nitro functionality was carried out concurrently with debenzylation producing amino lactone **84** which after hydrolysis and subsequent transamidation furnished (+)-7-deoxypancratistatin.

The total synthesis of (+)-7-deoxypancratistatin has also been achieved by Keck et al.[29d] in 1995 which utilized a radical cyclization strategy as shown in Scheme 9. The synthesis began with diol **85**, prepared from D-gulonolactone,[37] which after protection of the hydroxyl functionalities, reduction, and oxime formation gave hydroxy oxime **86**. Protection of the hydroxyl moiety as a methoxymethyl ether, selective removal of the silyl ether, and ensuing oxidation produced acid **87b** which was then converted into ester **88** under Mitsunobu conditions. Lithium halogen exchange of aryl bromide **88** gave the rearranged alcohol upon warming which was immediately oxidized to aldehyde **89**. Desilylation of aldehyde **89** followed by cyclization afforded ketone **90** after protection of the resulting lactol functionality. Ketone reduction followed by acylation furnished oxime **91** as the radical cyclization precursor. Formation of the radical derived from the thinocarbamate **91** and subsequent trapping by the oxime functionality generated the protected lactol **92** as a single stereoisomer which after acylation, desilylation, and



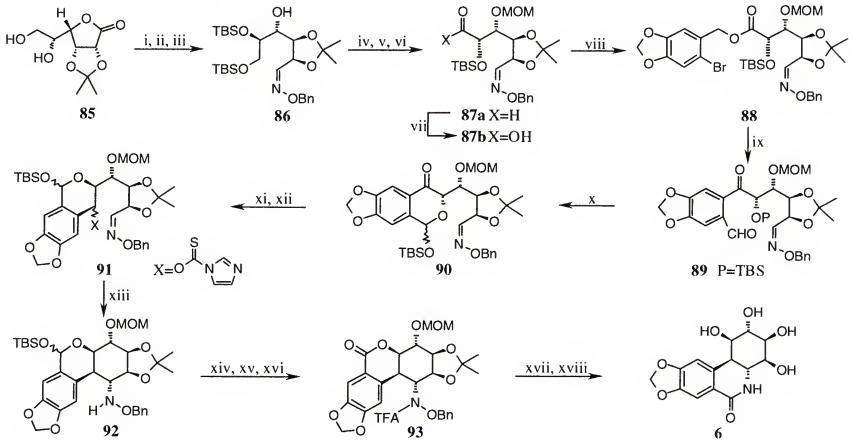
i. Ethyl acrylate, *p*–TSA; ii. NaOEt, EtOH, then H_2O; iii. $ClCO_2Et$, Et_3N, acetone; H_2O; iv. NaN_3, H_2O, then toluene, reflux; v. BF_3Et_2O; vi. Ac_2O, pyridine; vii. a) 1 N KOH, MeOH; b) NBS, THF; viii. DBU, pyridine; ix. 20 % aqueous NaOH, EtOH; x. 2,3-dihydropyran, *p*–TSA; xi. *m*CPBA, $CHCl_3$; xii. Diphenyldiselenide, EtOH, $NaBH_4$, then H_2O_2, xiii. a) Ac_2O, pyridine; b) *p*–TSA, AcOH, $MeOH_2$; xiv. OsO_4, pyridine; xv. 1 N KOH, MeOH.

Scheme 7. First Synthesis of (+/-)-7-Deoxypancratistatin



i. a) Isopropyl (6-bromo-3,4-(methylenedioxy))benzoate, *n*-BuLi, THF, -110 °C; b) nitroolefin **81**; ii. a) 50 % aqeous HOAc; reflux; b) K_2CO_3, MeOH; iii. H_2, Pd/C, MeOH; iv. K_2CO_3, MeOH, reflux.

Scheme 8. First Synthesis of (+)-7-Deoxypancratistatin



i. TBSCl, imidazole; ii. DIBAL, -78 °C; iii. $BnONH_2HCl$; iv. MOMCl, DIEA; v. HF·Pyridine; vi. TPAP, NMO, vii. $NaClO_2$, KH_2PO_4; viii. Ph_3P, DEAD, 4-bromo-5-(hydroxymethyl)-1,2-(methylenedioxy)benzene; ix. a) *n*-BuLi; b) TPAP, NMO; x. a) HF·Pyridine; b) TBSCl, imidazole; xi. $NaBH_4$, MeOH; xii. TCDI, DMAP, 1,2-dichloroethane; xiii. nBu_3SnH, AIBN, toluene; xiv. TFAA, pyridine, DMAP; xv. TBAF, THF; xvi. TPAP, NMO; xvii. SmI_2; xviii. a) Dowex H^+ resin;b) K_2CO_3, MeOH.

Scheme 9. Synthesis of (+)-7-Deoxypancratistatin

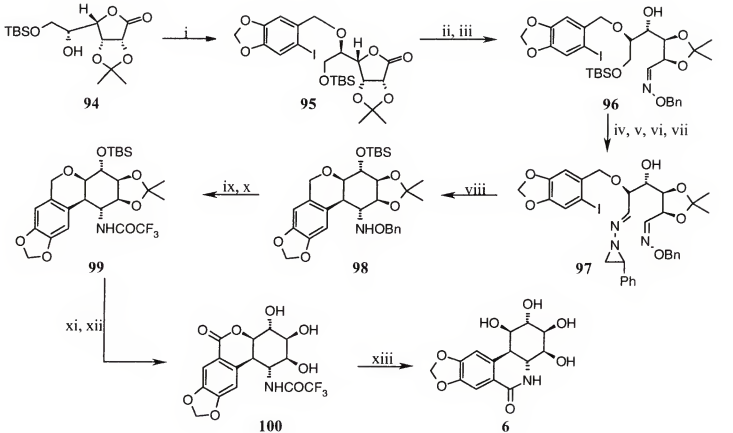
oxidation produced lactone **93**. Completion of the synthesis of (+)-7-deoxypancratistatin involved cleavage of the nitrogen oxygen bond, deprotection of the acetonide and methoxymethyl ether groups, and removal of the trifluoroacetamide group which occurred with concomitant lactone to lactam reorganization.

In a second generation synthesis, Keck and co-workers[29c] prepared (+)-7-deoxypancratistatin by way of an aryl radical cyclization of a tethered N-aziridinylimine as shown in Scheme 10. Alkylation of alcohol **94** with the trichloroacetimidate of 6-iodopiperonol genertaed aryl iodide **95** which was transformed into alcohol **96** following reduction of the lactone and oxime formation. A four step sequence converted alcohol **96** into N-aziridinylimine **97** as the cyclization precursor. Radical cyclization of aryl iodide **97** generated benzopyran **98** as a single diastereomer which upon clevage of the nitrogen oxygen bond and subsequent acylation gave trifluoroacetamide **99**. Oxidation of the benzylic position followed by simulataneous removal of the silyl ether and acetonide groups produced triol **100** which was converted to the alkaloid following deprotection of the trifluoroacetamide and ensuing lactone to lactam rearrangement.

Hudlicky and coworkers[29a,b] have also synthesized (+)-7-deoxypancratistatin in an asymmetric fashion beginning with diol **1b** which is obtained in enantiomerically pure form by whole cell biooxidation of bromobenzene.[30] Protection of the diol as the acetonide followed by reaction with methyl *p*–(nitrophenylsulfonyl)oxycarbamate generated aziridine **101**. Debromination under radical conditions afforded vinylaziridine **102** which was subsequently coupled with the higher order cyanocuprate derived from 4-bromo-1,2-(methylenedioxy)benzene to generate carbamate **103** which contains the carbocyclic skeleton of the alkaloid. Removal of the acetonide under standard conditions

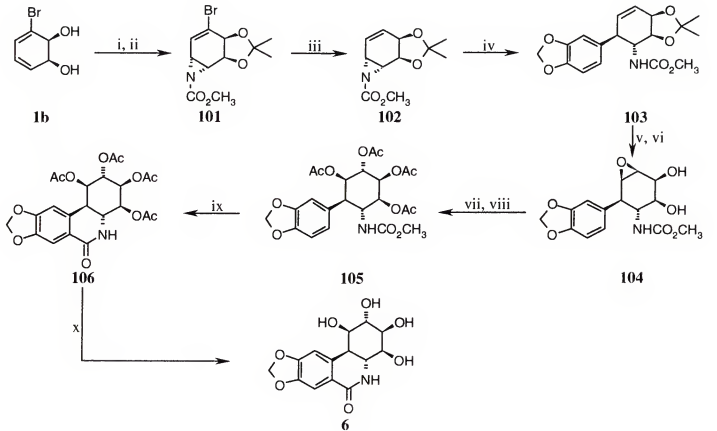
and subsequent hydroxyl-directed epoxidation of the olefin afforded epoxide **104** which was opened in a stereoselective fashion to provide tetracetate **105** following peracetylation. Bischler-Napieralski cyclization of carbamate **105** gave lactam **106** which upon deprotection furnished the alkaloid in 2.6 % overall yield and in 12 steps.

The laboratories of Chida[29c] have also completed a synthesis of (+)-7-deoxypancratistatin starting from D-glucose in which an intramolecular Heck reaction is used to construct the nucleus of the alkaloid as shown in Scheme 12. Protection of the known diol **107**[38] as the bis-(methoxymethyl) ether occurred concurrently with partial halide exchange to furnish the azides **108a** and **108b** as an inseparable mixture of compounds. Dehalogenation of the mixture of azides (**108a-b**) followed by Ferrier rearrangement of the resulting pyranoside afforded cyclohexanone **109** which was immediately converted into enone **110** via elimination. Luche reduction of enone **110** occurred in a stereoselective fashion to provide alcohol **111a** which was subsequently protected as its *p*-methoxybenzyl ether. Reduction of the azide in cyclohexene **111b** followed by condensation of the resulting amine with 6-bromopiperonylic acid under the protocol of Yamada et al.[39] gave aryl bromide **112** as the cyclization precursor. Following alkylation of the amide, intramolecular palladium catalyzed cyclization according to the conditions of Grigg et al.[40] furnished phenanthridone **113** which contains the core of the alkaloid. Stereoselective hydrogenation of olefin **113** followed by protection of the alcohol generated triflate **114**. Substitution of the triflate with acetate provided phenanthridone **115a** which was converted into alcohol **115b** following deprotection. Conversion of alcohol **115b** into its triflate and subsequent base induced elimination furnished the cyclohexene **116** following removal of the alcohol



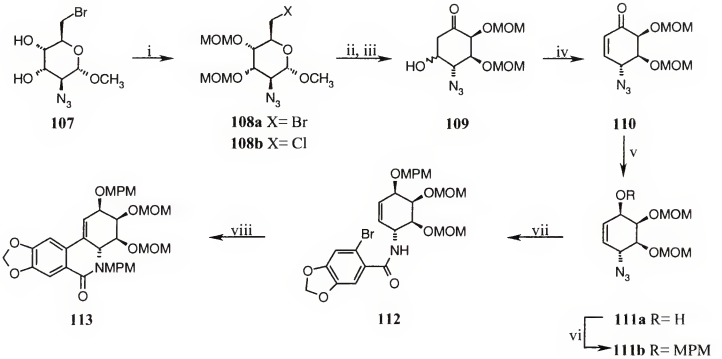
i. a) 6-iodopiperonol, NaH, Cl_3CN; b) TfOH, THF; ii. L-Selectride, CH_2Cl_2, -78 °C; iii. Pyridine, HCl H_2NOBn; iv. TBSOTf, 2,6-lutidine, CH_2Cl_2; v. HF·pyridine, THF; vi. TPAP, NMO; vii. 1-amino-2-phenylaziridine, EtOH, 0 °C; viii. Ph_3SnH, AIBN, benzene; ix. SmI_2; x. trifluoroacetic anhydride, pyridine, DMAP; xi. PCC, CH_2Cl_2, 55 °C; xii. BF_3Et_2O, $CHCl_3$; xiii. K_2CO_3, MeOH.

Scheme 10. Total Synthesis of (+)-7-Deoxypancratistin



i. DMP, *p*–TsOH, acetone; ii. $NaHCO_3$, H_2O, methyl (*p*–nitrophenylsulfonyl)oxycarbamate, $Bn(Et)_3NCl$, CH_2Cl_2; iii. nBu_3SnH, AIBN, THF; iv. a) 4-bromo-1,2-(methylenedioxy) benzene, *n*-BuLi, THF; b) CuCN; c) aziridine **102**; d) BF_3Et_2O; v. AcOH, THF, H_2O; vi. *t*–BuOOH, $VO(acac)_2$, benzene; vii. $C_6H_5CO_2Na$, H_2O; viii. Ac_2O, DMAP, pyridine; ix. Tf_2O, DMAP, CH_2Cl_2; x. $NaOCH_3$, MeOH.

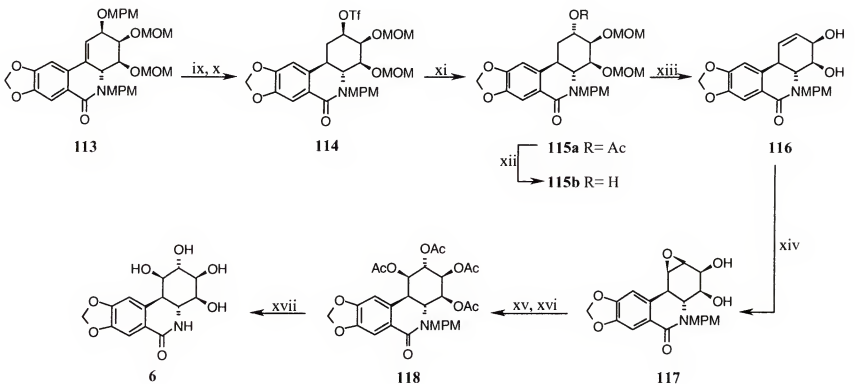
Scheme 11. Synthesis of (+)-7-Deoxypancratistatin



107 **108a** X= Br **108b** X= Cl **109** **110** **111a** R= H **111b** R= MPM **112** **113**

i. MOMCl, *i*-Pr_2Net, CH_2Cl_2; ii. DBU, toluene; iii. $Hg(OCOCF_3)_2$, acetone/H_2O; iv. MsCl, Et_3N, CH_2Cl_2; v. $NaBH_4$, $CeCl_3 7H_2O$, MeOH; vi. MPMCl, NaH, DMF; vii. a) LAH, ether; b) 6-bromopiperonylic acid, $(EtO)_2P(O)CN$, Et_3N, DMF; viii. a) MPMCl, NaH, DMF; b) $Pd(OAc)_2$, 1,2-bis(diphenylphosphino)ethane; TlOAc, DMF.

Scheme 12. Total Synthesis of (+)-7-Deoxypancratistatin (Part I)



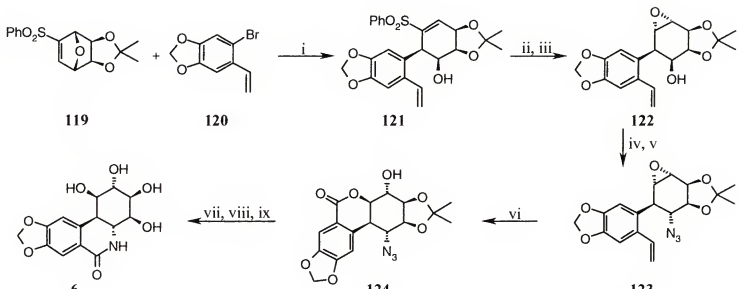
ix. H_2, Pd/C, EtOH/EtOAc; x. Tf_2O, pyridine; xi. KOAc, 18-crown-6, benzene; xii. THF-1 N aq. HCl; xiii. a) Tf_2O, pyridine; b) KOAc, 18-crown-6, benzene; c) THF-1 N aq. HCl, 50 °C; xiv. *m*CPBA, $(ClCH_2)_2$, pH = 8; xv. NaOAc, DMF/H_2O, 60 °C; xvi. Ac_2O, $ZnCl_2$; xvii. a)H_2, 5 % Pd/C, 1 N aq. HCl, EtOH b) NaOMe, MeOH.

Scheme 12. Total Synthesis of (+)-7-Deoxypancratistatin (Part II)

protecting groups. Hydroxyl-directed epoxidation of olefin **116** generated epoxide **117** stereoselectively which underwent *trans*-diaxial opening with acetate to afford polyacetate **118** following acetylation of the remaining hydroxyl groups. Removal of the *p*-methoxyl benzyl group followed by hydrolysis of the resulting polyacetate under basic conditions provided (+)-7-deoxypancratistin.

The most recent synthesis of (+)-7-deoxypancratistatin has been disclosed by Acena et al.[29f] in which addition of the lithium species derived from the functionalized aryl bromide **120** to vinyl sulfone **119**[105] afforded cyclohexenol **121** as illustrated in Scheme 13. Stereoselective epoxidation of the olefin followed by reduction of the sulfone with sodium amalgam produced epoxide **122** which was subsequently converted into epoxy azide **123** through a two step sequence. Oxidation of the styrene unit under ruthenium tetroxide catalysis generated the corresponding acid which underwent intramolecular cyclization via opening of the epoxide resulting in formation of lactone **124**. Simultaneous removal of the benzyl group and reduction of the azide via hydrogenolysis followed by ketal hydrolysis gave the corresponding amino triol which underwent a lactone to lactam rearrangement to furnish (+)-7-deoxypancratistatin in 19 steps and in 8 % overall yield.

The syntheses of (+)-7-deoxypancratistatin demonstrate the various stratagies which have been employed to construct the alkaloid. The construction of the C ring in the natural product and the stereochemical control of its substituents are issues which have been addressed via different methodologies in each of the syntheses of (+)-7-deoxypancratistatin. Additional stratagies aimed at preparing (+)-7-deoxypancratistatin in a more efficient manner continue to be explored in the future.



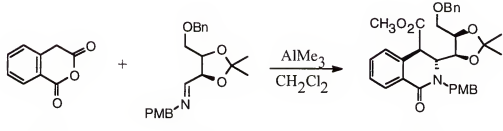
i. *n*-BuLi, THF/toluene, -78 °C; ii. *t*-BuOOH, *n*-BuLi, THF, -78 °C; iii. Na/Hg, MeOH/THF; iv. Tf_2O, pyridine, CH_2Cl_2; v. Bu_4NN_3, benzene; vi. $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$; vii. H_2, Pd/C 10 %, MeOH; viii. CF_3COOH; ix. K_2CO_3, MeOH.

Scheme 13. Total Synthesis of (+)-7-Deoxypancratistatin

Synthetic Approaches

The high degree of functionality and stereochemical features present in (+)-pancratistatin and (+)-7-deoxypancratistatin has resulted in a plethora of approaches towards efficiently synthesizing the phenanthridone system present in these natural products.[22] A number of these stratagies are outlined below and demonstrate the various synthetic methodologies which can be applied towards the synthesis of both of these alkaloids.

Clark and researchers[41] utilized a Lewis acid mediated condensation between anhydride **125** and imine **126** to produce lactam **127** as the major adduct. It was ratioinalized that the addition of triethylaluminum enriched the diastereoselectivity of the reaction through coordination of the Lewis acid to the imine during the course of the condensation. The resulting product, as shown in Scheme 14, contains four contiguous chiral centers representative of the stereochemistry in (+)-7-deoxypancratistatin.

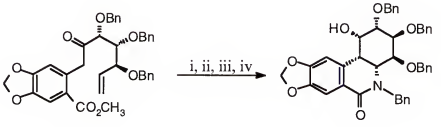


125 **126** **127**

Scheme 14. Clark's Strategy

Kallmerten and Thompson[42] successfully prepared a highly funtionalized phenanthridone system related to (+)-7-deoxypancratistatin in which an intramolecular aldol condensation served as the key step shown in Scheme 15. Formation of the C ring

was accomplished by a base induced aldol cyclization of the keto aldehyde derived from olefin **128** which ultimately gave phenanthridone **129** upon further chemical manipulation, an intermediate possessing four of the six stereogenic centers present in the C-ring of the alkaloid.



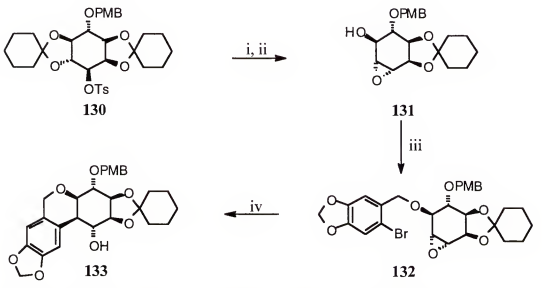
128 **129**

i. O_3, MeOH, -78 °C; Me_2S; ii. DBU, THF; iii. $PhCH_2NH_2$, PPTS; iv. $NaCNBH_3$, MeOH-HCl

Scheme 15. Kallmerten's Approach

Bender and Gauthier[43] have reported the preparation of a functionalized system related to (+)-7-deoxypancratistatin starting from *myo*-inositol as illustrated in Scheme 16. Selective deprotection of inositol derivative **130** followed by treatment of the ensuing diol with base provided alcohol **131** via internal displacement of the tosylate. Alkylation of alcohol **131** with 6-bromopiperonyl bromide gave aryl bomide **132**. Exposure of bromide **132** to *n*-butyllithium gave an intermediate aryllithiated species which cyclized onto the epoxide furnishing pentacycle **133**. The benzopyran **133** contains the correct absolute stereochemical configuration of the C-ring present within (+)-7-deoxypancratistatin. Both the introduction of nitrogen and oxidation of the benzylic

position are required in order to arrive at a more advanced intermediate which can undergo the transamidation process leading to construction of the phenaanthridone core.

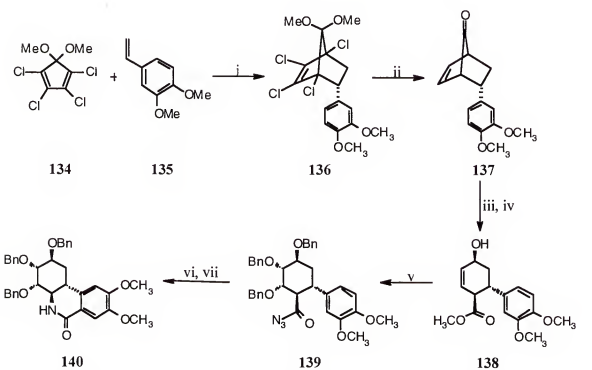


i. *p*-TsOH, EtOH, CH_2Cl_2; ii. NaOMe, MeOH; iii. NaH, 6-bromopiperonyl bromide, DMF; iv. *n*-BuLi, Et_2O, -78 °C

Scheme 16. Bender's Strategy

Mehta and Mohal[44] have recently described a stereoselective approach to densely functionalized cyclohexanoids related to the phenanthridone nucleus of (+)-7-deoxypancratistatin. The Diels-Alder reaction between 3,4-dimethoxystyrene (**135**) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**134**) produced *endo*-adduct **136** which was converted to aryl-7-norborneone **137** by way of reductive dechlorination and deketalization. A sequence involving Baeyer-Villiger oxidation of **137**, hydrolysis of the resulting mixture of lactones, and esterification gave rise to the allylic alcohol **138**. Acyl azide **139** was obtained from olefin **138** following dihydroxylation of the olefin, protection of the resulting diol, and functionalization of the ester group. Curtius

rearrangement of acyl azide **139** generated the intermediate carbamate which underwent cyclization to give the lactam **140** as shown in Scheme 17.

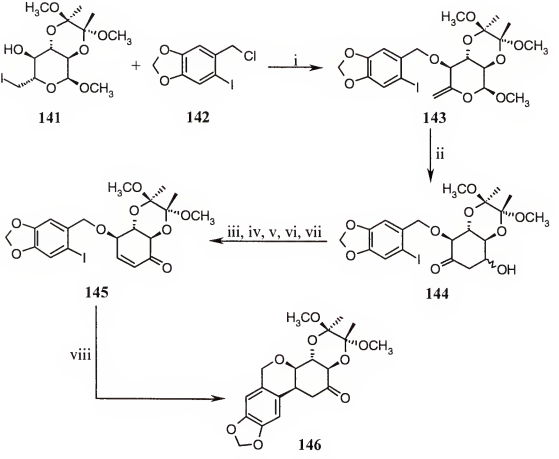


i. Δ; a) Na, NH_3; b) Amberlyst-15 resin, acetone iii. 30 % H_2O_2, AcOH; iv. NaOH, aq. THF then CH_2N_2; v. a) OsO_4; NMO, aq. acetone; b) NaH, BnBr; c) 20 % KOH/MeOH; d) $(COCl)_2$, pyridine, CH_2Cl_2 then NaN_3, acetone; vi. a) xylene, Δ; b) MeOH, Δ; vii. $POCl_3$, 80 °C.

Scheme 17. Mehta's Approach

The labs of Branchaud[45] have published an approach to the synthesis of (+)-7-deoxypancratistatin in which a palladium-mediated aryl-enone reductive cyclization gives rise to a highly fuctionalized benzopyran system as shown in Scheme 18. Alkylation of iodide **141** with the piperonol derivative **142** occurred with concomitant elimination of hydrogen iodide to ultimately furnish alkene **143**. A Ferrier rearrangement of alkene **143**

generated ketone **144** which was then converted into enone **145** in a five step sequence. Palladium catalyzed cyclization of aryl enone **145** afforded benzopyran **146** which is an advanced intermediate related to (+)-7-deoxypancratistatin.



i. NaH, DMF; ii. $Hg(OCOCF_3)_2$, acetone/H_2O; iii. TBDMSOTf, 2,6-lutidine; iv. $LiAlH(O^tBu)_3$; v. MsCl, Et_3N, CH_2Cl_2; vi. TBAF; vii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; viii. $Pd(OAc)_2$, PPh_3, Et_3N, THF

Scheme 18. Branchaud Strategy

In summary, both (+)-pancratistatin and (+)-7-deoxypancratistatin have been synthesized via unique synthetic sequences. In addition, many approaches aimed at efficiently preparing these natural products have been explored by various research

groups. Numerous less densely functionalized model systems have been synthesized which attests to the difficulty in synthesizing these alakaloids. The chemical features of these alkaloids, most notably the functionality and stereochemistry present in the C-ring, the *trans*- B-C amide ring junction, and the high degree of substitution in the aromatic A-ring, make efficient syntheses of these natural products a formidable challenge to the synthetic community.

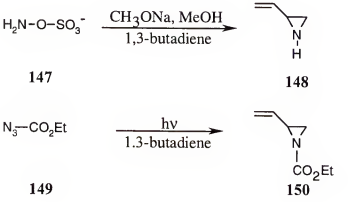
Vinyl Aziridine Synthesis

Aziridines compromise an important class of compounds displaying unique reactvity which can be applied in organic synthesis.[1] Like other three-membered rings, aziridines are highly strained; consequently, nucleophiles participate in ring opening reactions of aziridines. Such reactions of aziridines have attracted the attention of the synthetic community, and the applicabilty of these reactions in synthetic chemistry during the past three decades have been reviewed.[1a,46]

Introduction of additional functionality into aziridines enables for more unique chemistry to occur which can result in the construction of more complex systems. Vinylaziridines can be considered as a useful class of functionalized aziridines as a result of their ability to undergo various transformations[3] and rearrangements.[4] Unfortunately, methods for the generation of vinylaziridines are few; nevertheless, the synthetic community has obtained a renewed interest in developing methodologies for the efficient preparation of vinylaziridines because of the unique reactivity associated with these heterocycles.

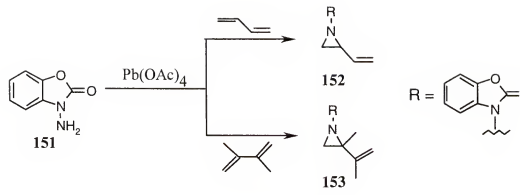
Preparation from Dienes by Nitrene Insertion

One of the more general methods employed for the synthesis of aziridines involves the reaction of an olefin with a nitrene which affords the corresponding aziridine. Since the disclosure of the addition of nitrene[47] and carboethoxynitrene[48a] to 1,3-butadiene to give vinylaziridines **148** and **150** as illustrated in Scheme 19, the addition of nitrenes to dienes has seen increased use in synthetic chemistry as a method for the preparation of vinylaziridines.



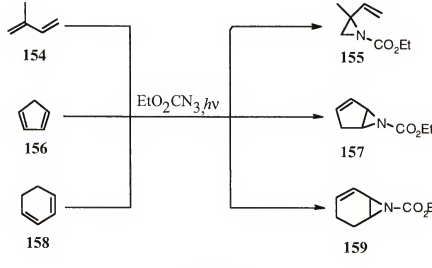
Scheme 19

Rees and Atkinson[49] have generated nitrenes by oxidation of 3-amino-benzoxazoline-2-one (**151**) mediated by lead tetraacetate and has trapped the resulting nitrenes with a variety of conjugated dienes to give vinylaziridines **152** and **153** as depicted in Scheme 20.



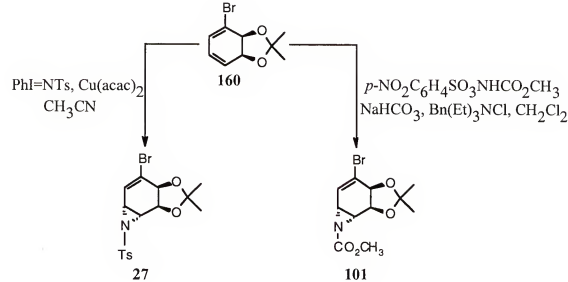
Scheme 20

The labs of Lwowski[48b] have studied the reaction of carboethoxynitrenes with 1,3-dienes and have also observed the formation of vinylaziridines. Generation of carboethoxynitrene via photolytic degradation of ethyl azidoformate in the presence of isoprene (**154**), cyclopentadiene (**156**), and 1,3-cyclohexadiene (**158**) produced the vinyl aziridines **155**, **157**, and **159** as shown below.



Scheme 21

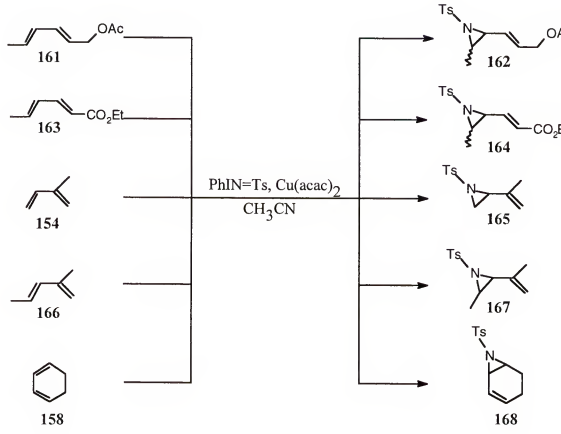
The formation of vinylaziridines through insertion of a nitrene species into a diene can generate chiral synthons which are useful in the asymmetric synthesis of important alkaloids. For example, the Hudlicky research group[5, 29a] has generated vinylaziridines **27** and **101**, key intermediates in the synthesis of members in the *Amaryllidaceae* family of alkaloids, via insertion of a nitrene species into the polarized 1,3-diene **160** as demonstrated in Scheme 22. The polarization of the diene via the electron withdrawing halogen controls the regioselectivity of the aziridination process; whereas, the stereoselectivity of the cycloaddition is dictated by steric factors attributed to the acetonide functionality.



Scheme 22

Knight and Muldowney[32c] have also studied the aziridination of several 1,3-dienes under copper catalysis[32a,b] using (N-tosylimino)phenyliodinane[31] as the nitrene source as illustrated in Scheme 23. In the case of unsymmetrical dienes **161** and **163**, formation of

aziridines **162** and **164** occurred at the more electron rich olefin; whereas, the regioselectivity of the aziridination of the electronically similar dienes **154** and **166** was governed by steric factors producing vinylaziridines **165** and **167** as the major products.



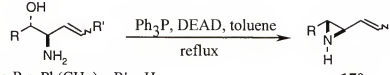
Scheme 23

Preparation from Amino Alcohol Derivatives

Another effective method by which vinylaziridines can be prepared involves intramolecular cyclization of amino alcohols following activation of the hydroxyl functionality. Moreover, the availability of enantiomerically pure amino alcohol

derivatives enables this methodology to be utilized in the preparation of chiral vinylaziridines which can be used in asymmetric synthesis.

As shown in Scheme 24, treatment of the *anti* amino alcohols **169a-b** under Mitsunobu conditions afforded the corresponding vinylaziridines **170a-b** in reasonable yields and in optically pure form.[50]

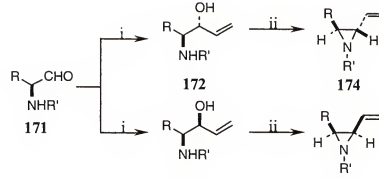


169a R = $Ph(CH_2)_2$, R' = H
169b R = $BnOCH_2$, R' = H

170a
170b

Scheme 24

In addition, the amino alcohols **172** and **173**, obtained as a diastereomeric mixture from the addition of vinyl organometallic reagents to amino aldehyde **171**, have been



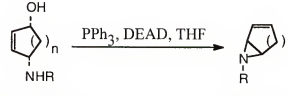
R = alkyl, aryl; R' = BOC, Ts

i. vinyl-M (M = Li, Mg, *etc.*); ii. PPh_3-$(NCO_2Et)_2$

Scheme 25

converted to the vinylaziridines **174** and **175** upon activation of the hydroxyl groups of the amino alcohols.[51]

The Olivo laboratory[52] has recently disclosed an efficient method for the synthesis of activated vinylaziridines upon exposing N-substituted 1,4-aminoalcohols to Mitsunobu conditions. The *cis*-1,4-aminoalcohols **176a-e** underwent an S_N2' type displacement following activation of the hydroxyl functionality to generate the vinylaziridines **177a-e** as shown in Scheme 26. An attractive feature of this methodology is the limited amount of oxazoline formation,[104] a common side reaction which occurs via nucleophilic attack of the carbonyl oxygen present in the carbamate functionality, as in **176d**.

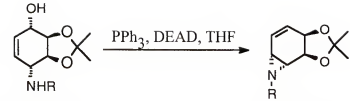


176a R = Bn, n = 1
176b R = Bn, n = 2
176c R = Bn, n = 3
176d R = CBz, n = 2
176e R = Ts, n = 2

177a R = Bn, n = 1
177b R = Bn, n = 2
177c R = Bn, n = 3
177d R = CBz, n = 2
177e R = Ts, n = 2

Scheme 26

In addition, this methodology has been utilized in the synthesis of optically pure vinylaziridnes. The chiral amino alcohol derivatives **178a-c**, when treated under Mitsunobu conditions, generated vinylaziridines **179a-c** in enantiomerically pure form as illustrated in Scheme 27.



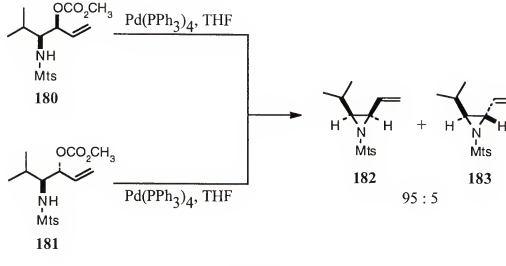
178a R = Bn
178b R = CBz
178c R = BOC

179a R = Bn
179b R = CBz
179c R = BOC

Scheme 27

Preparation via Transition Metal Catalysis

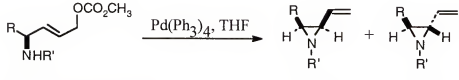
Another less utilized process which has been employed in the synthesis of vinylaziridines involves cyclization of amino functionalities onto unsaturated systems, such as alkenes, via transition-metal catalysis. For example, the N-protected methyl carbonates **180** and **181** were converted to the corresponding vinylaziridines **182** and **183** under palladium(0)-catalysis through a decarboxylative ring closure as depicted in Scheme 28.[51]



Scheme 28

The stereoselectivity associated with the intramolecular cyclization is an attractive feature of this synthetic methodology. An additional advantage of this methodology is that both isomeric carbonates **180** and **181** lead to the formation of vinylaziridines **182** and **183** in the same ratio.

Similarly, the allylic carbonates **184a-c** underwent cyclization upon exposure to catalytic amounts of palladium to provide the corresponding vinylaziridines **185a-c** and **186a-c** as shown in the following scheme.

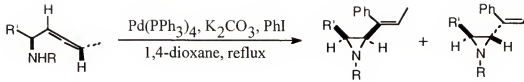


184a R = ^{i}Pr; R' = Mts
184b R = ^{i}Bu, R ' = Ts
184c R = Bn, R ' = Mts

185a **186a**
185b **186b**
185c **186c**

Scheme 29

Amino allenes have also been shown to undergo intramolecular cyclization via transition metal catalysis to furnish vinylaziridines in a stereospecific manner. For instance, the Ibuka group[53] has demonstrated that the amino allenes **187a-b** are readily converted into vinylaziridines **188a-b** and **189a-b** with good stereoselectivity upon exposure to palladium and an arylating agent as illustrated in Scheme 30.



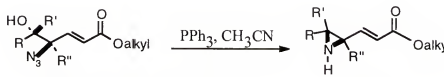
187a R' = Pr^i, R = Mts **188a** **189a** (84 : 16)
187b R' = Bn, R = Mts **188b** **189b** (85 : 15)

Scheme 30

Preparation from Functionalized Azides

Preparation from azido alcohols

Another method employed for aziridine synthesis involves a reductive cyclization sequence of functionalized azido alcohols; moreover, this concept has also been applied to the preparation of vinylaziridines. Wipf and Fritch[54] have reported a procedure for the syntheses of vinylaziridines **191a-b** from the azido alcohols **190a-b** via a Staudinger reaction as shown in Scheme 31.



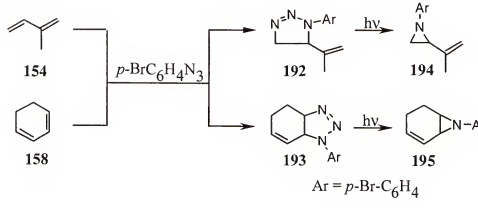
190a R = CH_3, R' = H, R" = H **191a**
190b R = H, R' = CH_3, R" = CH_3 **191b**

Scheme 31

Preparation from azidodienes

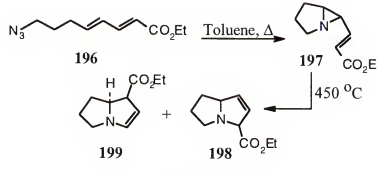
The [4 + 1] addition of azidodienes serves as a powerful means of constructing vinylaziridines which occurs via initial cycloaddition to form the intermediate triazoline

which upon extrusion of nitrogen gives the vinylaziridine. Scheiner[55] pioneered the dipolar 1,3-cycloaddition of azides with dienes; for instance, dienes such as isoprene (**154**) and 1,3-cyclohexadiene (**158**) were converted into triazolines **192** and **193** which upon photolysis gave vinylaziridines **194** and **195** as shown in Scheme 32.



Scheme 32

The azide diene cycloaddition has also been shown to occur in an intramolecular fashion; for instance, cycloaddition of azidodiene **196** afforded vinylaziridine **197** which



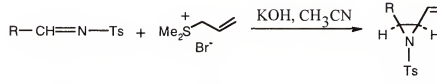
Scheme 33

upon pyrolysis gave a mixture of pyrrolines **198** and **199** with high regioselectivity as illustrated in Scheme 33.[56] Moreover, this methodology has been extensively used in the

construction of both the pyrrolizidine and indolizidine skeletons, both of which are useful in alkaloid synthesis.[56-57]

Preparation from Imines

Vinylaziridines have also been prepared by the addition of ylides to activated imines. The Dai group[58] has reported the formation of vinylaziridines **202** through the reaction of N-sulfonylimines **200** with sulfonium salt **201** under phase-transfer conditions as illustrated in Scheme 34. In addition to sulfonium salts, both telluronium and phosphorus allylic ylides have been utilized in the aziridination procedure.

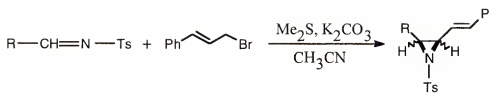


200 **201** **202**

R = C_6H_5, *p*-Cl-C_6H_4, *o*-CH_3O-C_6H_4, α-napthyl

Scheme 34

In a preliminary communication, the Dai laboratory[59] has shown that treatment of N-sulfonylimines, such as **203**, with cinnamyl bromide (**204**) under dimethyl sulfide catalysis generates the corresponding vinylaziridines **205** as a mixture of *cis* and *trans* isomers as shown in Scheme 35.

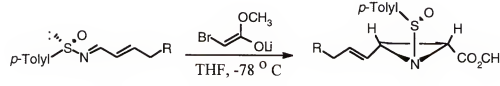


203 **204** **205**

R = *p*-Cl-C_6H_4, *p*-NO_2-C_6H_4, *o*-CH_3O-C_6H_4

Scheme 35

The Davis labs[60] have generated chiral vinylaziridines through a Darzens-type reaction between an enolate and enantiopure α,β-unsaturated sulfinimines. Condensation of the lithium enolate of methyl bromoacetate with sulfinimine **206** resulted in the formation of vinyl aziridine **207** in high optical purity as depicted in Scheme 36.



206 R = n-$C_{12}H_{25}$ **207**

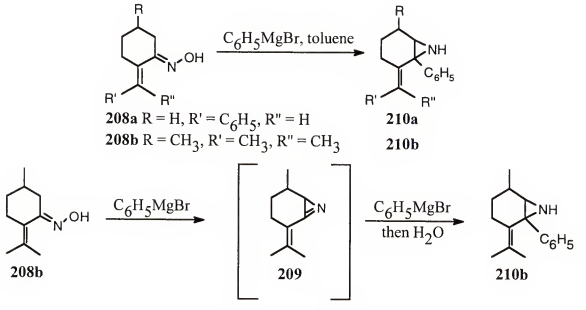
Scheme 36

Preparation by Miscellaneous Methods

Preparation from unsaturated oximes

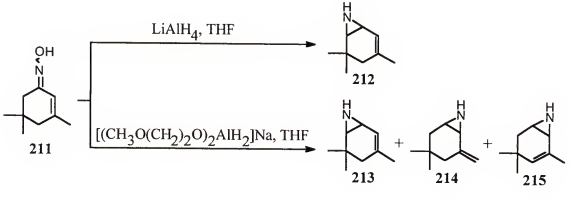
Laurent and Chaabouni[61] have shown that vinylaziridines can be synthesized by the addition of Grignard reagents to α,β-unsaturated oximes; for example, the unsaturated oximes **208a-b** upon treatment with various Grignard reagents gave vinylaziridines **210a-**

b. It has been postulated that this transformation proceeds via formation of azirine **209** which undergoes nucleophilic attack by a Grignard species to produce the vinylaziridine.



Scheme 37

Another method employed for the preparation of vinylaziridines involves a reductive cyclization of α,β-unsaturated oximes. Treatment of the unsaturated oxime **211**

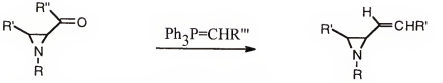


Scheme 38

with lithium aluminum hydride produced vinylaziridine **212**; whereas, the use of sodium bis(2-methoxyethoxy)aluminum hydride as the reducing agent gave rise to the isomeric vinylaziridines **213-215** as shown in Scheme 38.[62]

Preparation from aziridinyl aldehydes/ketones

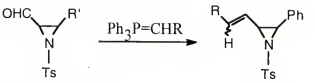
A few reports pertaining to the preparation of vinylaziridines by Wittig olefination of the appropriately functionalized aldehydes have been disclosed. For instance, the labs of Vessière[63] have converted a number of 2-formylaziridines (**216a-c**) into the corresponding vinylaziridines **217a-c** via a Wittig reaction as shown in Scheme 39.



216a R = $C(CH_3)_3$, R' = H, R'' = CH_3, R''' = CH_2 **217a**
216b R = CH_2Ph, R' = H, R'' = Ph, R''' = CH_2 **217b**
216c R = $C(CH_3)_3$, R' = H, R'' = H, R''' = $CH{=}CO_2C_2H_5$ **217c**

Scheme 39

In addition, the Oshima research group[64] has generated the N-tosyl vinylaziridines **219a-c** from the requisite aldehydes **218a-c** by way of a Wittig olefination as illustrated in Scheme 40.



218a R = $CH{=}CH_2$, R = CH_3 **219a**

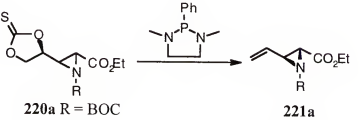
218b R = $CH{=}CHC_3H_7$, R = CH_3 **219b**

218c R = $C(CH_3){=}CH_2$, R = CH_3 **219c**

Scheme 40

Preparation from aziridinyl diols

An additional strategy which has been used for the synthesis of vinylaziridines involves installation of the olefin through elimination of an appropriately functionalized diol moiety present within the molecule. Jähnisch[65] has reported the preparation of vinylaziridines by way of this strategy as depicted in Scheme 41; that is, the thiocarbonate derivatives **220a-b**, obtained from the requisite diols, were transformed into vinylaziridines **221a-b** via the Corey procedure.[66]



220a R = BOC **221a**

220b R = Bn **221b**

Scheme 41

In summary, the utility of vinylaziridines in organic chemistry has increased during the past few decades; consequently, the synthetic community has experienced a

renewed interest in the efficient preparation of vinylaziridines. A variety of substrates can be utilized to efficiently prepare vinylaziridines, such as dienes, amino alcohols, imines and azides. In addition, many of the precursors used for the synthesis of vinylaziridines are available in enantiopure form thus providing a means of generating optically pure vinylaziridines which are useful in asymmetric synthesis.

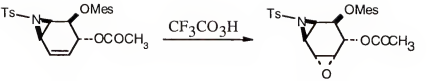
Epoxyaziridine Synthesis

Epoxyaziridines serve as valuable intermediates in synthetic organic chemistry, yet limited methodology presently exists for the preparation of such compounds. The presence of two strained ring systems, each of which possess the capability of being opened independently under appropriate conditions, allows for the controlled introduction of nucleophilic components in both a stereospecific and regioselective manner. The unique reactivity associated with epoxyaziridines can be used for the construction of rather complex systems in an expeditious manner which validates the importance of these compounds to the synthetic community.

Preparation from Functionalized Olefins

One method by which epoxyaziridines are prepared involves oxidation of olefinic aziridines in order to generate the oxirane ring. The Prinzbach labs[67b] have prepared epoxyaziridine **223** from aziridinyl olefin **222** via peroxytrifluoroacetic acid mediated epoxidation as depicted in Scheme 42.

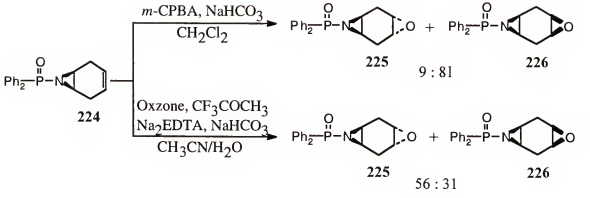
In a similar tansformation, the oxidation of diphenylphosphinoyl aziridine **224** was successfully accomplished using either *m*-CPBA or methyl(trifluoromethyl)dioxirane as the oxidizing agent to yield epoxyaziridines **225** and **226** as a mixture of stereoisomers



222 **223**

Scheme 42

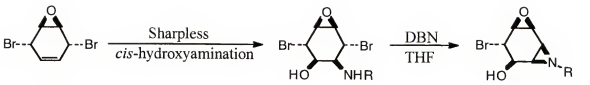
as depicted in Scheme 43.[68]



Scheme 43

Preparation via Internal Substitution

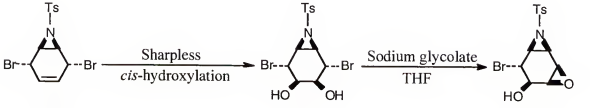
Another method by which epoxyaziridines have been prepared involves internal displacement of a suitably placed leaving group, a process which can be used to form either the aziridine or the oxirane ring. The Prinzbach group[67] has performed a *cis*-hydroxyamination of epoxyalkene **227** by Sharpless and Herranz's protocol[69] generating amino alcohol **228** stereoselectively as shown in Scheme 44. Treatment of amino alcohol **228** with base afforded epoxyaziridine **229** via an internal displacement of bromide.



227 228 229

Scheme 44

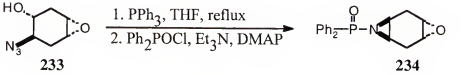
Similarly, dihydroxylation of aziridinyl olefin **230** gave rise to diol **231** which upon exposure to sodium glycolate underwent internal displacement of bromide to furnish epoxyaziridine **232** as shown in the following scheme.



230 231 232

Scheme 45

The synthesis of epoxyaziridines via internal displacement has also been reported by O'Brien and Pilgram[68] in which epoxyaziridine **234** is generated upon reduction of



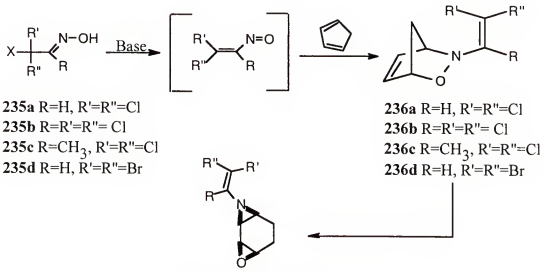
233 234

Scheme 46

epoxy azide **233**,[70] alcohol activation, and ensuing cyclization as shown in Scheme 46.

Preparation from Oxazines

The Viehe group [71] has reported an efficient methodology for the prepartion of epoxyaziridines in a stereospecific manner by way of the epoxyepimination of N-vinyl oxazines. For example, the oxazines **236a-d**, generated by the [4+2] cycloaddition of cyclopentadiene with the corresponding nitrosoalkenes, isomerize at room temperature to give the epoxyaziridines **237a-d** as depicted in Scheme 47.[71b,c]



235a R=H, R'=R"=Cl
235b R=R'=R"= Cl
235c R=CH_3, R'=R"=Cl
235d R=H, R'=R"=Br

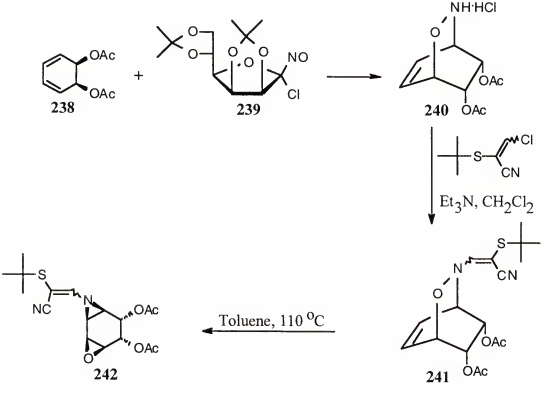
236a R=H, R'=R"=Cl
236b R=R'=R"= Cl
236c R=CH_3, R'=R"=Cl
236d R=H, R'=R"=Br

237a R=H, R'=R"=Cl
237b R=R'=R"= Cl
237c R=CH_3, R'=R"=Cl
237d R=H, R'=R"=Br

Scheme 47

In addition, the Viehe labs[71a,c,d] have utilized this synthetic methodology for the preparation of optically pure epoxyaziridines through the use of a carbohydrate based nitroso derivative. For instance, cycloaddition of the α-chloronitroso mannose derivative

239 with the optically pure cyclohexadiene **238** results in formation of the chiral oxazine **240** which was subsequently alkylated with β-chloro-α-*tert*-butylthioacrylonitrile to generate the N-functionalized oxazine **241**. Upon thermolysis, oxazine **241** rearranges in a stereospecific fashion to provide epoxyaziridine **242** which contains four asymmetric centers. The transfer of chirality to all four dienic carbon atoms of cyclohexadiene **238** through this epoxyepimination process validates the utility of this methodology in asymmetric synthesis; moreover, the preparation of chiral aminocyclitols from epoxyaziridines generated in this manner demonstrates the applicability of the epoxyepimination procedure to organic synthesis.



Scheme 48

The importance of epoxyaziridines in organic synthesis stems from the presence of two strained rings, each of which can be selectively opened under appropriate conditions. The renewed interest in efficiently preparing epoxyaziridines in addition to the unique reactivity associated with these molecules has provided the synthetic community with a valuable intermediate which can be used for the synthesis of a variety of compounds.

Nucleophilic Ring Openings of Aziridines

Aziridines are an attractive class of compounds which contain enormous potential in organic synthesis as a result of the unique reactivity associated with these heterocycles; moreover, the chemistry of aziridines is dominated by ring opening recactions which occur as a result of the inherent ring strain present in these molecules. More recently, ring opening reactions of chiral aziridines have been used for the preparation of enantiomerically pure compounds as intermediates in the asymmetic synthesis of biologically active molecules.[2]

In a general sense, aziridines can be categorized into two groups based on the nature of the substituent on nitrogen.[72] Activated aziridines possess an electron-withdrawing functionality which allows for conjugative stabilization of the developing negative charge on nitrogen occurring during the transition state of nucleophilic ring opening reactions; consequently, such reactions can take place in the absence of catalysis. Nonactivated aziridines, on the other hand, lack the ability to stabilize the developing negative charge on nitrogen which results from nucleophilic ring opening and therefore usually require acid catalysis in order to faciltate ring opening reactions.

"Activated"
R = COR, CO_2R, SO_2R, *etc.*

"Nonactivated"
R = H, alkyl, aryl, *etc.*

Figure 6. Activated and Nonactivated Aziridines

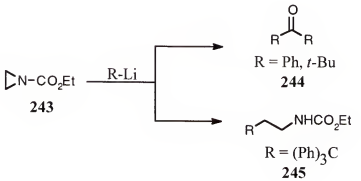
Both activated and nonactivated aziridines are susceptible to ring opening reactions; moreover, the vast amount of research has demonstrated that both the appropriate choice of functionality on nitrogen and the substitution pattern on the carbon framework of the aziridine dictate the regio- and stereoselectivity of ring opening reactions. Aziridines have undergone ring opening reactions with a host of noncarbon nucleophiles, such as oxygen based nucleophiles[73], halide ions[74] and nitrogen based nucleophiles[75] among others. This section will focus on perhaps the most useful reaction of these strained heterocyles which is the ring opening reactions of aziridines by carbon centered nucleophiles resulting in carbon-carbon bond formation under relatively mild conditions.

Intermolecular Ring Openings

Openings by organometallic reagents

The reaction of organometallic reagents with aziridines which affords ring opened products has seen increased use by the synthetic community since the initial work of Hassner and Kascheres[76] in which aziridinecarbamate **243** was allowed to react with a variety of alkyllithium species. As illustrated in Scheme 49, both benzyllithium and *t*-

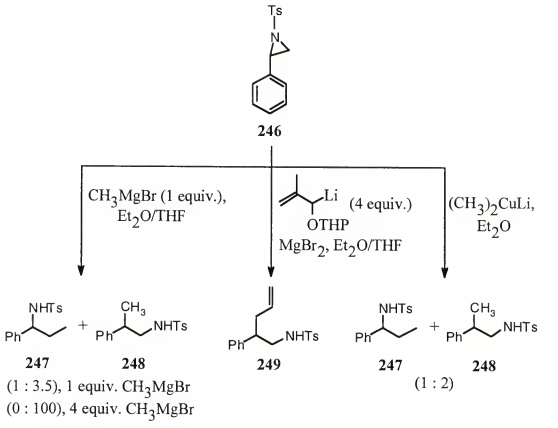
butyllithium resulted in the formation of ketones **244** via carbonyl attack; whereas, trityllithium only furnished carbamate **245** arising from nucleophilic ring opening.



Scheme 49

These results suggest that the course of the reaction is controlled by nucleophilicity rather than basicity; that is, the stronger nucleophiles tend to react at the carbonyl functionality while weaker nucleophiles are inclined to attack the ring carbon of the aziridine.

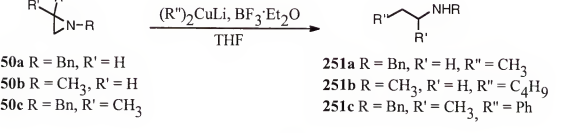
The Kozikowski labs[77] have studied the regiochemical preference in the attack of organometallic reagents on unsymmetrical aziridines. For example, an array of organometallic nucleophiles, including organolithium species, Grignard reagents, and cuprates, were allowed to react with aziridine **246** resulting in formation of the ring opened products **247**-**249** as depicted in the Scheme 50. The regioselectivity of the ring opening reactions is dictated by electronic factors; that is, transfer of the alkyl substituent occurs at the carbon atom which best accomodates partial carbonium ion character. In the case of reactions involving excess Grignard reagent, the ring opening becomes completely regiospecific as a consequence of the ability of the excess Grignard species to act as a Lewis acid which activates the aziridine even further to nucleophilic attack at the



Scheme 50

more electrophilic benzylic center.

The ability of Lewis acids to promote ring opening reactions of aziridines by organometallic species has been displayed by Eis and Ganem.[78] As illustrated below, a



250a R = Bn, R' = H
250b R = CH_3, R' = H
250c R = Bn, R' = CH_3

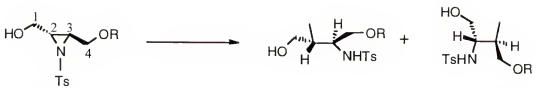
251a R = Bn, R' = H, R" = CH_3
251b R = CH_3, R' = H, R" = C_4H_9
251c R = Bn, R' = CH_3, R" = Ph

Scheme 51

variety of primary and secondary amines **251a-c** were successfully prepared via boron-triflouride diethyletherate mediated nucleophilic ring opening of the unactivated aziridines **250a-c** by several diorganocopperlithium reagents.

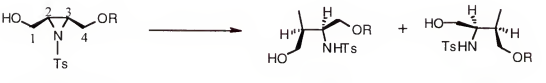
The laboratories of Tanner[1a,79] have reported the regioselective opening of 2,3-ariridinyl alcohols by various cuprates and other alkyl-transfer reagents (Scheme 52). Nucleophilic addition of either Gilman reagents or Lipshutz cyanocuprates to *trans*-aziridinyl alcohols **252a-b** generated tosylamides **253a-b**; whereas, addition to the *cis*-aziridinyl alcohols **254a-b** gave tosylamides **255a-b** with satisfactory C-2 regioselectivity (Tables 1 and 2). The use of trimethylaluminum as the nucleophilic reagent, on the other hand, resulted in excellent C-3 regioselectivity furnishing the primary tosylamides **253b** and **255b** as the major products. The C-2 regioselectivity of the cuprate additions in the ring opening reactions results from initial complexation of the reagent to the C-1 hydroxyl group followed by intramolecular attack at C-2 of the aziridine ring. The use of trimethylaluminum as the nucleophilic species results in C-3 regioselectivity as a result of intramolecular delivery of the methyl group to the more proximal (C-3) carbon following formation of the complex between trimethylaluminum and the alkoxy group (C-4) of the aziridine. The control of the regiochemistry resulting from the attack of organometallic reagents on such aziridinyl alcohols is dictated by the substituent on the oxygen atom at C-1; that is, the substituent on the oxygen atom can be used to direct attack of the organometallic agent to C-2 via complexation with the attacking species or to C-3 by exerting steric effects.

The Sweeney group[80] has described the ring opening reactions of enantiopure N-diphenylphosphinyl aziridines with various of carbon nucleophiles. As shown in Scheme



252a R = Bn
252b R = Si^{t}BuMe$_2$

253a **253b**



254a R = Bn
254b R = Si^{t}BuMe$_2$

255a **255b**

Scheme 52

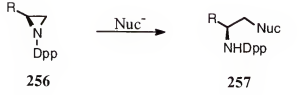
Table 1. Regioselective Opening of *Trans*-2,3-Aziridinyl Alcohols (**252a-b**)

Substrate	Reaction Conditions	**253a:253b**	Yield (%)
252a	$LiMe_2Cu$, Et_2O, -20 °C	>99:1	80
252b	$LiMe_2Cu$, Et_2O, -20 °C	>99:1	98
252a	Li_2Me_2CuCN, THF, -20 °C	92:8	81
252b	Li_2Me_2CuCN, THF, -20 °C	>99:1	92
252a	$AlMe_3$, toluene, 75 ° C	<1:99	71
252b	$AlMe_3$, toluene, 75 ° C	15:85	82

Table 2. Regioselective Opening of *Cis*-2,3-Aziridinyl Alcohols (**254a-b**)

Substrate	Reaction Conditions	**255a:255b**	Yield (%)
254a	Li_2Me_2CuCN, THF, -20 °C	79:21	73
254b	Li_2Me_2CuCN, THF, -20 °C	88:12	68
254b	$LiMe_2Cu$, Et_2O, -20 °C	78:22	87
254a	$AlMe_3$, toluene, 75 ° C	<1:99	92
254b	$AlMe_3$, toluene, 75 ° C	33:66	60

53, nucleophilic attack occurs at the least hindered carbon of aziridines **256** to provide diphenylphosphinylamides **257** in a selective manner.



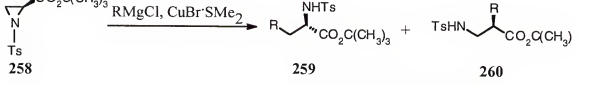
256 **257**

Scheme 53

Table 3. Ring Opening of N-Diphenylphosphinyl Aziridines (**256**) by Nucleophiles

R	Nucleophile	Reaction Conditions	Yield (%)
$PhCH_2$	Me_2CuLi	THF, -78 °C to 0 °C	87
Me_2CHCH_2	Me_2CuLi	THF, -78 °C to 0 °C	53
$PhCH_2$	CH_3CH_2MgBr	CuBr·SEt_2, THF, reflux	73
Me_2CHCH_2	C_6H_5MgBr	CuBr·SEt_2, THF, reflux	84
$PhCH_2$	$Me_2CHMgBr$	CuBr·SEt_2, THF, reflux	88

Baldwin and researchers[81] have studied the ring opening reactions of aziridine-2-carboxylate esters by organometallic reagents as illustrated in Scheme 54. Treatment of N-tosylaziridinylcarboxylate **258** with various organometallic reagents gave rise to a mixture of tosylamides **259** and **260** which are useful for amino acid synthesis.

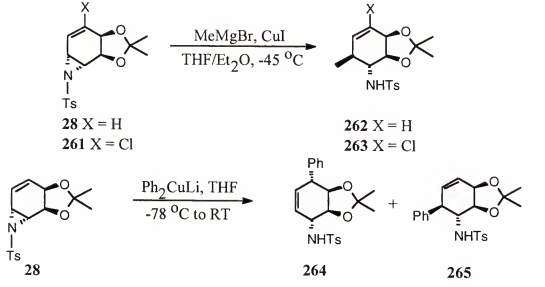


258 **259** **260**

R = Me, *i*-Pr, *n*-Bu, Et

Scheme 54

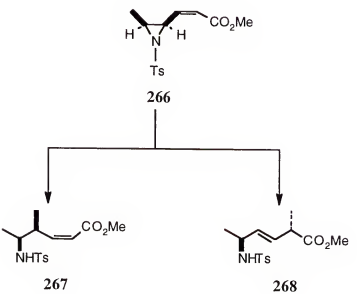
A study of the modes of reactivity in the ring opening reactions of a series of vinylaziridines by different organometallic species has been reported by the Hudlicky group.[5] Reaction of vinylaziridines **28** and **261** with Grignard species gave rise to tosylamides **262** and **263** via S_N2 opening; whereas, reaction of vinylaziridine **28** with lithium diphenylcuprate afforded tosylamides **264** and **265** resulting from both S_N2 and S_N2' opening as depicted in Scheme 55.



Scheme 55

The laboratories of Ibuka[3b] have also investigated the regiochemical outcome from the addition of various organometallic species to vinylaziridines. Reaction of the diastereomerically pure β-aziridinyl-α,β-enoate **266** with several organometallic reagents afforded tosylamides **267** and **268** as illustrated in Scheme 56. Moreover, these ring opening reactions proceed with high regio- and stereoselectivity in which tosylamide **268**

is the major product resulting from an *anti* S_N2' addition of the organometallic species relative to the C_γ-N bond.



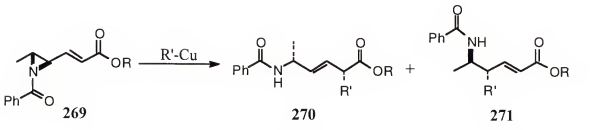
Scheme 56

Table 4. Ring Opening Reactions of Vinylaziridine **266** by Organometallics

Compound	Organometallic Reagent	**267:268**	Yield (%)
266	Me_2ZnLi, 30 mol % CuCN	4:90	94
266	Me_2ZnLi, 30 mol % CuCN	3:81	84
266	Me_2ZnLi, 30 mol % CuCN	4:94	98
266	MeCu(CN)Li	6:93	99

Wipf and Fritch[54] have examined the reaction of vinylaziridines with a variety of organocuprate reagents. Treatment of vinylaziridine **269** with several organocuprates under boron-triflouride diethyletherate catalysis provided benzamides **270** as the major product formed via S_N2' attack of the nucleophile along with minor amounts of benzamides **271** as shown in Scheme 57. In addition, the reaction between the

organocuprate species and the vinylaziridines occurred with a high degree of diastereoselectivity (98 to 95 % de) which is a consequence of an *anti* S_N2' attack of the nucleophile.



269 **270** **271**

Scheme 57

Table 5. Ring Opening Reactions of Vinylaziridine **269** by Organometallics

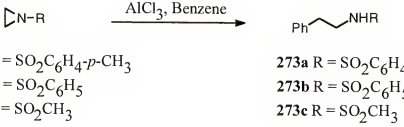
Cuprate (Additive)	R'	**270**:**271**	Yield (%)
MeCu (BF_3)	Me	62:6	68
MeCu(CN)Li (BF_3)	Me	60:3	63
BuCu (BF_3)	Bu	69:14	83
PhCu (BF_3)	Ph	32:0	32

Openings by aromatic systems

Aromatic systems also can act as nucleophiles in ring opening reactions of aziridines resulting in an aminoethylation of the aromatic group, but such types of Friedel-Crafts reactions are somewhat rare. These reactions usually only occur under conditions involving double activation[82] of the aziridine; that is, the reaction proceeds under acid catalysis only with aziridines containing electron withdrawing groups.

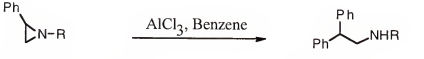
Various N-sulfonated aziridines have undergone ring opening reactions with aromatic molecules as reported by the Stamm research group.[83] As shown in Scheme 58, aziridines **272a-c** were opened to produce sulfonamides **273a-c** in the presence of

benzene under Lewis acid activation. In the case of the unsymmetrical aziridines **274a-c**, ring opening reactions proceeded in a regioselective manner generating sulfonamides **275a-c** in which nucleophilic attack took place at the benzylic site.



272a R = $SO_2C_6H_4$-*p*-CH_3
272b R = $SO_2C_6H_5$
272c R = SO_2CH_3

273a R = $SO_2C_6H_4$-*p*-CH_3
273b R = $SO_2C_6H_5$
273c R = SO_2CH_3

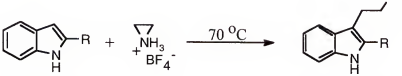


274a R = $SO_2C_6H_4$-*p*-CH_3
274b R = $SO_2C_6H_5$
274c R = SO_2CH_3

275a R = $SO_2C_6H_4$-*p*-CH_3
275b R = $SO_2C_6H_5$
275c R = SO_2CH_3

Scheme 58

Indoles have also been shown to act as nucleophiles in ring opening reactions of activated aziridines under Lewis acid catalysis. Pfeil and Harder[84] have alkylated both indole and 2-methylindole with the readily accessible[85] aziridinium tetrafluoroborate **277**



276a R= H
276b R = CH_3

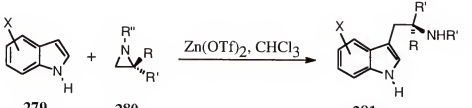
277

278a R = H
278b R = CH_3

Scheme 59

furnishing the aminoalkylated indoles **278a-b** as depicted in Scheme 59.

Optically pure tryptophan derivatives have been prepared by Sato and Kozikowski[86] via methodology involving the ring opening of chiral aziridines by various substituted indoles. Treatment of the aziridinylcarboxylates **280** with zinc triflate in the presence of indoles **279** gave rise to the trytophan derivatives **281** in which alkylation occurred at the 3 position of the indole.



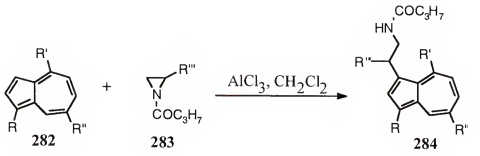
279 **280** **281**

Scheme 60

Table 6. Ring Opening Reactions of Optically Pure Aziridines (**280**) By Indoles

Entry	X	R	R'	R''	Yield (%)
1	H	H	CO_2Bu	Cbz	64
2	5-OCH_3	H	CO_2Me	Cbz	35
3	4-NO_2	H	CO_2Bn	Cbz	4
4	5-CH_3	H	CO_2Bn	Cbz	57
5	H	H	CO_2Me	BOC	41

Kurokawa and Anderson[87] have also performed Friedel-Crafts alkylation reactions of several activated aziridines using azulene derivatives as the nucleophilic component. Aluminum chloride mediated opening of butanoylaziridines **283** by the substituted azulenes **282** afforded the azulenylethanamine derivatives **284** as illustrated in Scheme 61.



Scheme 61

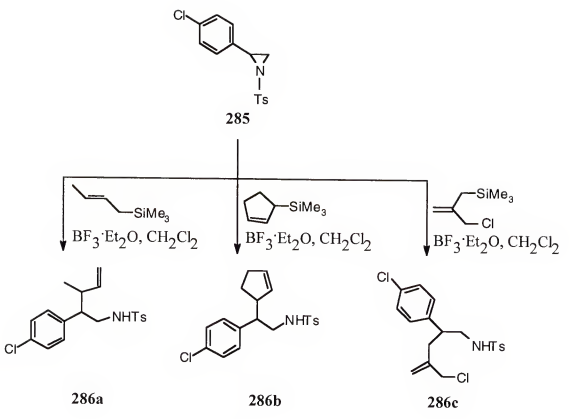
Table 7. Friedel-Crafts Alkylation of Azulenes with Activated Aziridines

Entry	R	R'	R''	R'''	Yield (%)
1	H	H	H	H	21
2	CH_3	CH_3	$CH(CH_3)_2$	CH_3	57
3	H	H	H	CH_3	20
4	CH_3	CH_3	$CH(CH_3)_2$	H	8

Openings by allylsilanes

Allylsilanes serve as ambient nucleophiles in the ring opening reactions of aziridines; however, few examples of intermolecular allylsilane additions to aziridines have been reported. The use of allylsilanes as nucleophiles is advantageous to organometallic reagents since the conditions for the ring opening reactions usually allow for a broader range of functionality present on the substrates.

The intermolecular addition of a variety of allylsilanes to activated aziridines has been examined by Schneider et al.[88] The reaction of several allylsilanes with N-tosylaziridine **285** under boron triflouride diethyletherate catalysis produced the corresponding γ-amino olefins **286a-c** in a regioselective manner as illustrated in Scheme 62.



Scheme 62

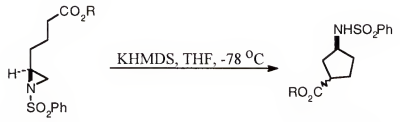
Intramolecular Ring Openings

More recently, intramolecular cyclizations have seen increased use in synthetic methodology in which a tethered nucleophilic species undergoes a ring opening reaction with an aziridine. In many cases, such intramolecular processes proceed stereoselectively which allows for the synthesis of functionalized carbocyclic products.

Anionic cyclizations

The first example of an intramolecular ring opening reaction of an aziridine was disclosed by Rapoport et al.[89] in course to the synthesis of carbocyclic nucleotides. Treatment of esters **287a-b** with base generated the corresponding enolates which

underwent an intramolecular cyclization onto the activated aziridine to produce cyclopentanes **288a-b** as shown in Scheme 63.



287a R = Me
287b R = ^{t}Bu

288a R = Me
288b R = ^{t}Bu

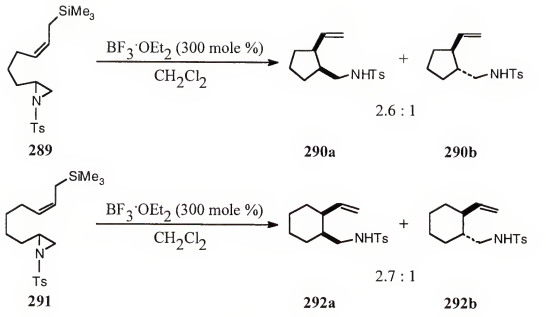
Scheme 63

Lewis acid mediated cyclizations

The intramolecular cyclization of aziridines with allylsilanes mediated by Lewis acids provides a means of generating functionalized cyclopentanes and cyclohexanes. Bergmeier and Seth[90] have successfully synthesized cyclopentanes **290a-b** and cyclohexanes **292a-b** as mixtures of stereoisomers from aziridines **289** and **291** following Lewis acid activation of the aziridine as depicted in Scheme 64.

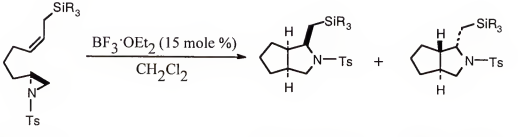
In addition, the Bergmeier labs[91] have found that treatment of the aziridines **293a-b** with smaller amounts of Lewis acid gave tosylamides **294a-b** and **295a-b** as the major products formed via a [3+2] cycloaddition as illustrated in Scheme 65.

Clearly the ring opening reactions of aziridines by carbon centered nucleophiles are an important class of reactions in synthetic organic chemistry; moreover, this methodology has been used in the preparation of a variety of biologically active compounds including alkaloids, amino acid analogs, and β-lactam antibiotics. These



Scheme 64

heterocycles can be generated in enantiomerically pure form and thus can be regarded as key intermediates for the asymmetric synthesis of organic molecules. The suitable choice



293a R = CH_3
293b R = $Ph(CH_3)_2$

294a R = CH_3
294b R = $Ph(CH_3)_2$

295a R = CH_3
295b R = $Ph(CH_3)_2$

Scheme 65

of substituents on the carbon and nitrogen atoms of the aziridine allows for excellent stereospecific and regioselective additions of nucleophiles making aziridines an invaluable class of compounds in the field of organic synthesis.

CHAPTER 3
DISCUSSION

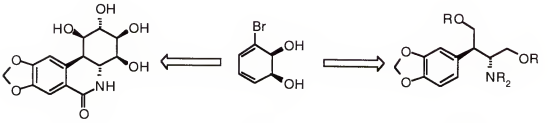
Introduction

Both (+)-pancratistatin (**7**) and (+)-7-deoxypancratristatin (**6**) are *Amaryllidaceae* alkaloids which exhibit anticancer activity[19,20] and have shown promise as therapeutic agents. Unfortunately, these natural products are present in low abundance from their natural resources; for example, (+)-pancratistatin was isolated from *Pancratium littorale* (~0.000091 %, dry weight) by Pettit and researchers.[14a] The limited supply of these alkaloids has impeded further biological evaluation which would provide insight with respect to structure-activity relationships. The scarce availability of these natural products and their inherent structural complexity have resulted in extensive synthetic work in this area as demonstrated by several syntheses of (+)-pancratistatin[27,28] and (+)-7-deoxypancratistatin.[29]

The challenge posed by all synthetic endeavors aimed at preparing these alkaloids resides in the construction of the six contiguous asymmetric centers of the highly funtionalized C-ring. The structural motifs present within these natural products which complicate synthetic approaches include the high degree of substitution of the aromatic A-ring, the stereochemistry of the functionalities embedded along the C-ring, and the *trans* B-C amide ring junction. These combined structural features must be thoroughly addressed when designing a synthetic approach to the synthesis of (+)-pancratistatin (**7**),

(+)-7-deoxypancratistatin (**6**), or their related analogs.

The availability of the *cis*-dihydrocyclohexadiene (**1b**) as a chiral synthon has given the synthetic community a means of incorporating asymmetric methodology in the preparation of important intermediates. Issues of diastereoselectivity are dictated by either directing or steric factors associated with the diol functionality; whereas, aspects of regioselectivity of initial functionalizations are determined by the polarization of the diene system. The remarkable ability of this system to control the stereo- and regiochemical outcome of synthetic transformations serves as the basis for an approach to the preparation of (+)-7-deoxypancratistatin (**6**) in addition to several truncated analogs (**296**) as shown below.



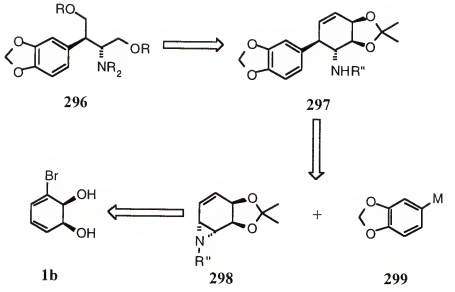
6 **1b** **296**

Figure 7. Synthetic Targets

Retrosynthetic Analysis for Truncated Analogs

The synthesis of the truncated analogs (**296**) was viewed retrosynthetically as shown in Scheme 66. The functionalized cyclohexene **297** serves as the precursor to the truncated analogs (**296**) via complete oxidative degradation of the cyclohexenyl ring. Stereo- and regioselective addition of aryl nucleophile **299** to vinylaziridine **298** should afford cyclohexene **297** in which the *trans* relationship between the aromatic system and

the amino functionality is established. Vinylaziridine **298** in turn can be obtained by selective chemical manipulation of the diene system present within *cis*-dihydrocyclohexadiene **1b**.

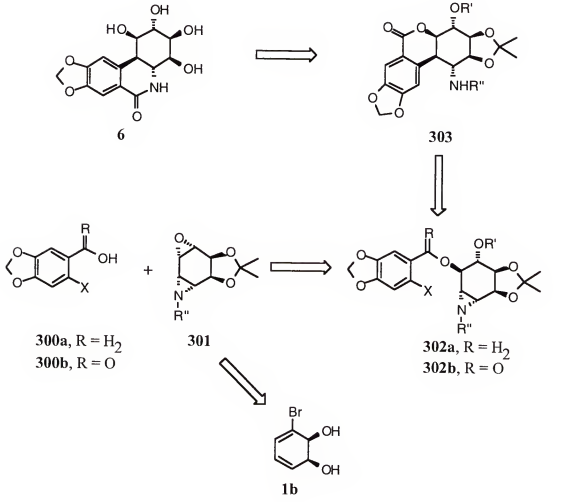


Scheme 66. Retrosynthetic Analysis (Truncated Analogs)

Retrosynthetic Analysis for (+)-7-deoxypancratistatin

As illustrated in Scheme 67, it was envisioned that (+)-7-deoxypancratistatin (**6**) could be obtained via a transamidation protocol involving hydrolysis of lactone **303** and concomitant formation of the amide bond. The lactone **303** in principle could be generated from either ether **302a** or ester **302b** via two different synthetic routes. In the ether approach, the highly functionalized aziridine **302a** could be transformed into lactone **303** through a sequence comprising of intramolecular cyclization of the aromatic system onto the aziridine ring followed by benzylic oxidation of the activated benzopyran unit. For the ester approach, it was envisioned that intramolecular cyclization of the

aziridine **302b** could give rise to lactone **303** directly in which the oxidation sequence is avoided. The ester approach utilizes a more deactivated aromatic system as the nucleophilic component which may encumber the cyclization process; whereas, in the ether approach, such deactivation of the piperonyl moiety is not an issue. Coupling of the



Scheme 67. Retrosynthetic Analysis ((+)-7-Deoxypancratistatin)

suitable piperonyl species (**300a** or **300b**) with epoxyaziridine **301** under conditions in which the oxirane is selectively opened should furnish the functionalized aziridines (**302a**

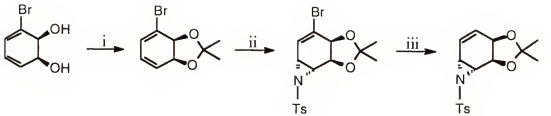
or **302b**) as the cyclization precursors. The epoxyaziridine **301** can be aquired from *cis*-dihydrocyclohexadiene **1b** through selective funtionalization of the diene system.

Synthesis of Vinylaziridines

As illustrated by the retrosynthetic analyses which describe the approaches to both the synthesis of (+)-7-deoxypancratistatin (**6**) (Scheme 67) and several related truncated analogs (**296**) (Scheme 66), the manipulation of functionalized chiral aziridines serves as the basis for the preparation of these molecules. Two different methodologies which both begin with bromocyclohexadiene-*cis*-diol **1b** have been used for the preparation of chiral vinylaziridines, and these synthetic routes will be discussed in the following sections.

Preparation from Dienes

As depicted in Scheme 68, vinylaziridine **28** has been synthesized by functionalization of the diene system present within diol **1b** according to recently reported procedures.[5] Protection of the halodiene **1b** with 2,2-dimethoxypropane under *p*-toluenesulfonic acid catalysis furnished acetonide **160** in essentially quantitative yield. Treatment of diene **160** with Yamada's iodonium ylide **304**[31] following the protocol of Evans et al.[32a] afforded N-tosyl aziridine **27** albeit in rather poor yield; nonetheless, recovery of acetonide **160** and resubjection to the aziridination conditions increased the overall productivity of the process to approximately 50 % overall yield. Dehalogenation of vinylaziridine **27** was readily achieved under typical conditions (nBu_3SnH, AIBN, THF, reflux) to provide vinylaziridine **28** in 78 % yield.



1b **160** **27** **28**

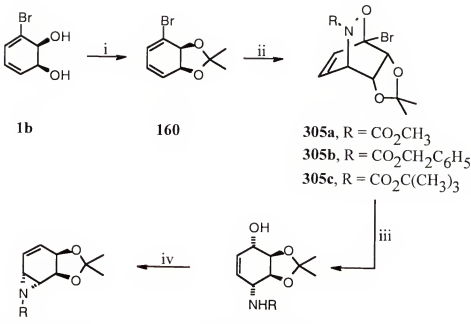
i. 2,2-dimethoxypropane, *p*-TsOH, acetone; ii. PhI=NTs (**304**), $Cu(acac)_2$, CH_3CN, 22 % (over two steps); iii. nBu_3SnH, AIBN, THF, 78 %

Scheme 68

Preparation from Amino Alcohols

In addition, several vinylaziridines have been successfully prepared from amino alcohol derivatives as disclosed by the Olivo group[52] through a S_N2' type displacement under Mitsunobu conditions. As shown in Scheme 69, oxazines **305a-c** can be prepared via a regio- and stereospecific hetero Diels-Alder cycloaddition between acetonide **160** and nitroso dienophiles which are generated as transient intermediates through the oxidation of hydroxamic acids ($NaIO_4$, $MeOH/H_2O$). Reductive cleavage of the nitrogen-oxygen bond present within oxazines **305a-c** using Keck's aluminum amalgam procedure[92] gives rise to the *cis*-1,4-aminoalcohols **306** and **178b-c** in good yields. Treatment of the *cis*-1,4-aminoalcohols under Mitsunobu[93] conditions (PPh_3, DEAD, THF) furnished the corresponding 2-vinylaziridines **102** and **179b-c**. The preparation of vinylaziridines from 1,4-aminoalcohols under Mitsunobu conditions (Scheme 69) is much improved to the copper-catalyzed aziridination of dienes (Scheme 68) in terms of the yield of the reaction, the ease of purification of the product, and the versatiltiy in choice of N-activating groups. Moreover, N-carbamoyl aziridines are advantageous to

N-tosyl aziridines with regard to deprotection of the amino functionality since removal of the tosyl group is difficult and frequently requires harsh conditions.[94]



i. 2,2,-dimethoxypropane, *p*-TsOH, acetone; ii. RNHOH, $NaIO_4$, $MeOH/H_2O$; 65-74 % iii. Al(Hg), THF/H_2O; 66-70 % iv. PPh_3, DEAD, THF; 64-84 %

Scheme 69

Synthesis of Truncated Analogs of (+)-7-deoxypancratistatin

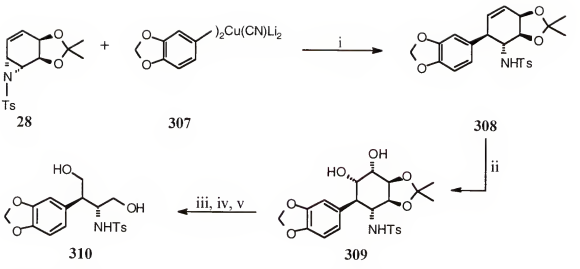
With an efficient preparation of various N-substituted 2-vinylaziridines (**298**) in hand, the synthesis of several truncated analogs of (+)-7-deoxypancratistatin was investigated. Following the methodology reported by the Hudlicky labs[27b,29a] in the synthesis of (+)-7-deoxypancratistatin (**6**), regio- and stereocontrolled ring opening of N-

tosyl aziridine **28** with the higher order cyanocuprate **307** afforded primary sulfonamide **308** as illustrated in Scheme 70.

Initially, the direct oxidative cleavage of the olefin bond in sulfonamide **308** by ozonolysis was attempted; however, this reaction failed to effectively cleave the olefin and produced a complex mixture of products. With no success in effecting oxidative degradation of the cyclohexenyl ring through ozonolysis, the dihydroxylation of the olefin in sulfonamide **308** was examined with the hope of cleaving the resulting diol by conventional methods. Unfortunately, dihydroxylation of the olefin using osmium tetraoxide as the oxidizing agent met with failure even after prolonged reaction times; nevertheless, oxidation of cyclohexene **308** under ruthenium catalysis[95] occurred stereospecifically and furnished diol **309** in 75 % yield.

With sufficient amounts of diol **309** in hand, the stage was set for investigation of the oxidative degradation of the functionalized cyclohexyl ring. Accordingly, ketal hydrolysis of diol **309** under acidic conditions (TFA, THF/H_2O), complete oxidative cleavage of the resultant tetrol ($NaIO_4$, acetone/H_2O), and reduction of the ensuing dialdehyde ($NaBH_4$, MeOH) gave rise to tosylamide **310** which possesses the skeletal framework of the desired truncated analogs.

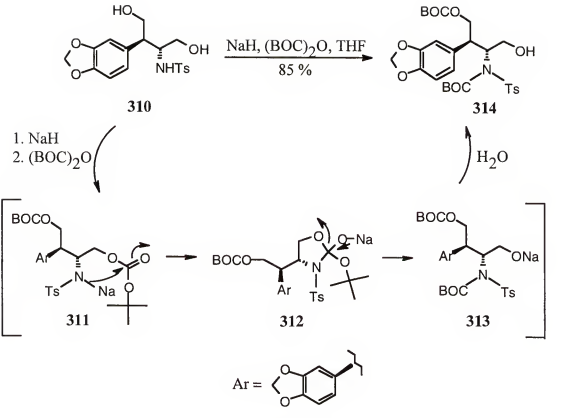
In order to obtain the fully deprotected truncated analog, tosylamide **310** had to be reduced to the corresponding amine. Although the tosyl group is an effective protecting group for amines as a result of its tolerance to various acidic and basic conditions, cleavage of sulfonamides by reported methods in the literature has proven to be troublesome.[94]



i. BF_3Et_2O, THF, -78 °C; 21 %; ii. $RuCl_3 3H_2O$, $NaIO_4$, EtOAc/CH_3CN, 75 %; iii. TFA/THF/H_2O; iv. $NaIO_4$, acetone/H_2O; v. $NaBH_4$; MeOH; 60 % (over 3 steps)

Scheme 70

To this end, the deprotection of tosylamide **310** was first examined under reductive conditions including sodium/naphthalene[96] and samarium (II) iodide.[94] Disappointingly, both sets of detosylation conditions failed to produce the amine of interest; therefore, tosylamide **310** was subjected to acylation conditions (NaH, $(BOC)_2O$, THF) based on a report in the literature on the decreased reduction potential of N-acyl sulfonamides[97] and their conversion to carbamates.[98] Interestingly, treatment of tosylamide **310** with greater than three equivalents of both sodium hydride and di-*tert*-butyl dicarbonate provided alcohol **314** as shown in Scheme 71. The sole production of alcohol **314** is postulated to form via the intermediate dicarbonate **311** in which transfer of the acyl group from the carbonate to the deprotonated tosylamide occurs.

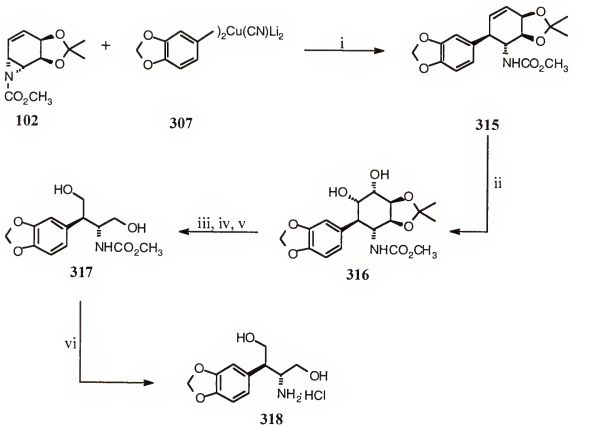


Scheme 71

Unfortunately, treatment of tosylamide **314** with excess sodium/anthracene[99] in an attempt to remove the tosyl group failed to deliver the corresponding carbamate which warranted consideration of a more easily removed amino protecting group.

Difficulties encountered with the removal of the tosyl group shifted the focus of the synthesis to the coupling of the higher order cyanocuprate **307** with vinylaziridine **102** under the notion that deprotection of the methyl carbamate would be more facile. To this end, coupling of cyanocuprate **307** with vinylaziridine **102** mediated by boron triflouride diethyletherate proceeded as reported by the Hudlicky group[29a] resulting in formation of carbamate **315** as depicted in Scheme 72. Similar to the methodology carried out with sulfonamide **308**, oxidation of the olefin under ruthenium tetroxide

catalysis[95] provided diol **316** which was converted to carbamate **317** via a three step sequence consisting of deprotection of the acetonide, complete oxidative degradation of the resulting tetrol, and reduction of the ensuing dialdehyde. Base induced hydolysis of carbamate **317** and subsequent decarboxylation occured smoothly resulting in formation of the free amine which was isolated as the hydrochloride salt **318** under standard conditions.



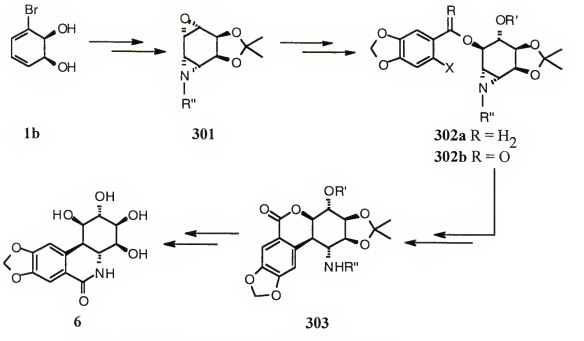
i. BF_3Et_2O, THF, -78 °C; 18 %; ii. $RuCl_3 3H_2O$, $NaIO_4$, EtOAc/CH_3CN, 69 %; iii. TFA/THF/H_2O; iv. $NaIO_4$, acetone/H_2O; v. $NaBH_4$; MeOH; 45 % (over 3 steps); vi. 20 % aq. KOH, MeOH then HCl, MeOH; 82 %

Scheme 72

In summary, several truncated analogs structurally related to the alkaloid (+)-7-deoxypancratistatin were successfully prepared in which a stereoselective and regioselective opening of different vinylaziridines serves as the key step. Besides the simplified "seco analogs," there has been no detailed structure-activity investigation with respect to (+)-pancratistatin or (+)-7-deoxypancratistatin.[100] The analogs discussed in the previous section were synthesized with the purpose of gaining an understanding of possible structure-activity relationships; unfortunately, screening of all truncated derivatives showed no indication of biological activity similar in magnitude to that displayed by (+)-pancratistatin or (+)-7-deoxypancratistatin. Interestingly, derivative **314** displayed some activity and gave indication of cancer cell line inhibition with GI_{50} values of 5.3 μg/ml against pancreas-a BXPG-3 and 8.5 μg/ml with lung NCI-H460.[101]

Intramolecular Aziridine Cyclization Approach

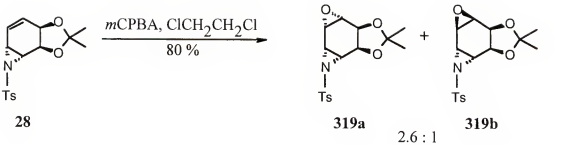
With the availabilty of various N-substituted vinylaziridines, an effort toward completing a second generation synthesis of the alkaloid (+)-7-deoxypancratistatin was undertaken. As described earlier and illustrated in Scheme 73, a highly functionalized aziridine (**302a-b**) in which a tethered piperonyl substituent capable of undergoing intramolecular cyclization was required for the projected synthesis of the alkaloid. Successful intramolecular cyclization would ultimately lead to the generation of lactone **303** which upon hydrolysis and recyclization would give the phenanthridone core of the alkaloid. Therefore, the construction of the key intermediates, aziridines **302a-b**, became the initial focus of the synthetic endeavor.



Scheme 73. Projected Synthesis of (+)-7-deoxypancratistatin

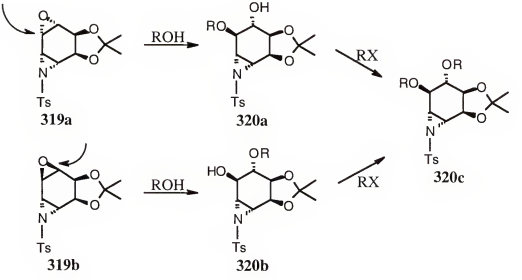
Vinylaziridine Oxidation

At the onset of the study, intramolecular cyclization of the piperonyl group following formation of an intermediate aryl organometallic species was proposed based on Bender and Gauthier's related intramolecular cyclization of an *o*-tethered lithiated piperonyl moiety onto an epoxide.[43] The epoxidation of the olefin in vinylaziridine **28** was examined since it was anticipated that opening of the epoxide by a nucleophilic piperonyl derivative could be selectively achieved leaving the aziridine functionality intact. The attempted oxidation of tosyl aziridine **28** with *m*CPBA at room temperature gave only trace amounts of the desired epoxide even after prolonged reaction times; however, treatment of tosyl aziridine **28** with *m*CPBA in 1,2-dichloroethane at reflux produced an inseparable mixture of α and β epoxaziridines **319a-b** (2.6:1) as illustrated in Scheme 74.



Scheme 74

Although the oxidation of vinylaziridine **28** gives an inseperable mixture of α and β epoxyaziridines **319a-b**, both isomers can be used for subsequent reactions. As illustrated in Scheme 75, *trans*-diaxial opening of the oxirane in either isomer **319a** or **319b** with an appropriately substituted alcohol would generate the alcohols **320a** and **320b** respectively. Alkylation of the hydroxyl functionality in both **320a** and **320b** with the same group rendered into an electrophile would provide aziridine **320c**, an intermediate in which both oxygens contain identical functionality.

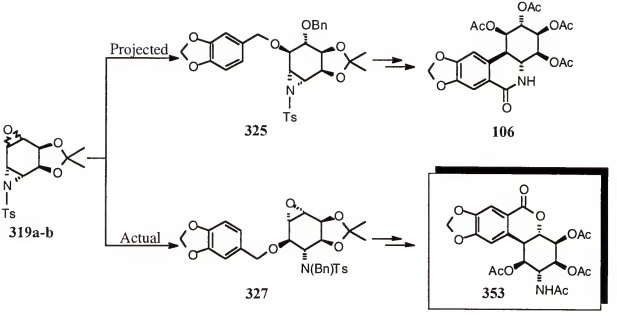


Scheme 75

Such "redundant operations" greatly improve the practicality of such a synthetic sequence because no attention need be paid to either the control of stereochemistry at the intermediate stage or to the separation of the isomeric epoxyaziridines.[106]

Projected Versus Actual Synthetic Sequence

With the mixture of epoxyaziridines **319a-b** in hand, the construction of the key cyclization precursors as described in Scheme 73 was begun following previous reports internal to the research group regarding the selective opening of the oxirane ring within epoxyaziridines **319a-b** by carboxylate salts under basic conditions.[107] *The selective opening of the epoxide moiety present in the mixture of epoxyaziridines **319a-b** did not occur as anticipated; rather, as shown in Scheme 76, a nucleophilic attack on the aziridine ring by the piperonylic species occurred exclusively, only ascertained at the end of the synthesis when tetraacetate **353** was isolated and identified.*



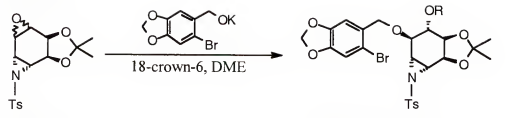
Scheme 76

In the following sections, the projected transformations believed to have been performed in the presumed path to the synthesis of (+)-7-deoxypancratistatin (**6**) will be compared with a description of the actual results, although these were NOT known until the very end of the synthesis following an unsuccessful match between tetracatates **353** and **106** (Scheme 88).

Intramolecular Anionic Cyclization Approach

With a sufficient amount of the mixture of N-tosyl epoxyaziridines **319a-b** available, the anticipated selective opening of the epoxide moiety with various piperonyl derivatives was examined. Based on an assumed precedent obtained within the research group,[107] it was envisioned that opening of the epoxide by piperonylic species would be more facile than attack on the aziridine ring and thus lead to the preferential formation of the corresponding alcohols. Initially, the potassium salt of 2-bromopiperonol was reacted with epoxyaziridines **319a-b** which was expected to result in a regio- and stereoselective opening of the oxirane thus producing alcohol **321** as depicted in the projected path, Scheme 77. Ensuing benzylation of the hydroxyl group believed to arise from opening of the epoxide appeared to afford ether **322**. The potassium salt of 2-bromopiperonol was first used as the nucleophilic species based on the prospect that transmetalation of the aryl unit in **322** would be followed by cyclization of the intermediate organometallic species onto the activated aziridine ring. Unfortunately, it was subsequently discovered that nucleophilic attack of the aziridine ring by the potassium salt of 2-bromopiperonol occurred exclusively generating tosylamide **323** which was converted into N-benzyl tosylamide **324** as illustrated in the actual sequence, Scheme 77.

Projected:



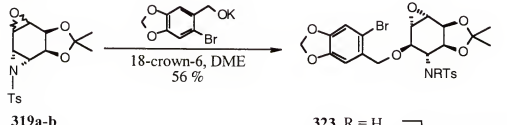
319a-b

321, R = H

322, R = Bn

NaH, BnBr, *n*-Bu_4NI, THF

Actual:



319a-b

323, R = H

324, R = Bn

NaH, BnBr, *n*-Bu_4NI, THF 90 %

Scheme 77

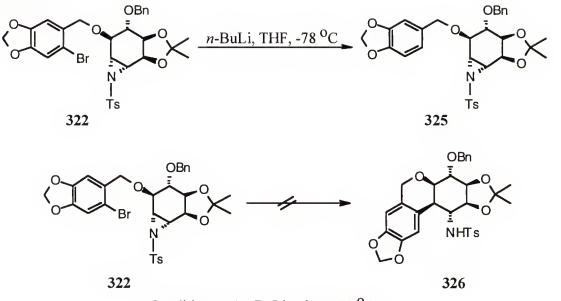
Standard nuclear magnetic resonance spectrosopic techniques failed to unambiguously discriminate between aziridine **321** of the projected path and epoxide **323** of the actual synthetic sequence (Scheme 77). For example, the remarkable similarity in the chemical shifts and splitting patterns for the aziridine and oxirane methine protons in epoxyaziridines **319a-b** complicated the analysis of the ^1H NMR spectrum. The inability to adequately distinguish between aziridine **321** and epoxide **323** in combination with the assumed precedent obtained within the research group[107] regarding the selective opening of the oxirane within epoxyaziridines **319a-b** by piperonyl nucleophiles led to the initial structure misassignment.

Several transmetalation conditions were examined in an effort to bring about the intramolecular cyclization of postulated aziridine **322** which, if successful, would furnish tosylamide **326** as shown in the projected path, Scheme 78. The tosylamide **326** represents an advanced intermediate in which the six contiguous chiral centers of the C-ring in the alkaloid are established. The conditions employed to effect transmetalation of the piperonyl functionality with either *t*-butyllithium or *n*-butyllithium in diethyl ether failed to afford tosylamide **326** and only resulted in extensive decomposition. However, treatment of the presumed tosylamide **322** with either *t*-butyllithium or *n*-butyllithium in THF or DME did not result in decomposition but appeared to only furnish the dehalogenated derivative **325** as illustrated in the projected path, Scheme 78. The sole observation of reduction of the aryl bromide under these conditions confirmed the formation of the intermediate organometallic species, and it was anticipated that intramolecular cyclization may proceed under prolonged reaction times or at elevated temperatures. Unfortunately, attempts to invoke cyclization under these conditions all met with failure and only resulted in debromination of the aryl ring. In actuality, the transmetalation conditions were implemented on epoxide **324** which failed to bring about the intramolecular cyclization; moreover, treatment of epoxide **324** with *n*-butyllithium or *t*-butyllithium in THF or DME generated the debrominated derivative **327** as depicted in the actual sequence, Scheme 78.

Intramolecular Lewis Acid Cyclization Approach

As a result of the encountered difficulties with successfully acheiving intramolecular cyclization under transmetalation conditions, an attempt to bring about the cyclization via Lewis acid catalysis was investigated based on reports of intramolecular

Projected:

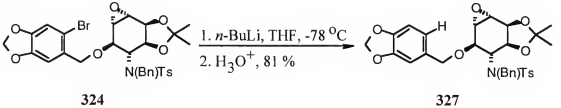


322 325

322 326

Conditions: a) *t*-BuLi, ether, -78 °C
b) *t*-BuLi, CuCN, ether, -78 °C
c) *n*-BuLi, ether, -78 °C
d) Mg, I_2, THF

Actual:

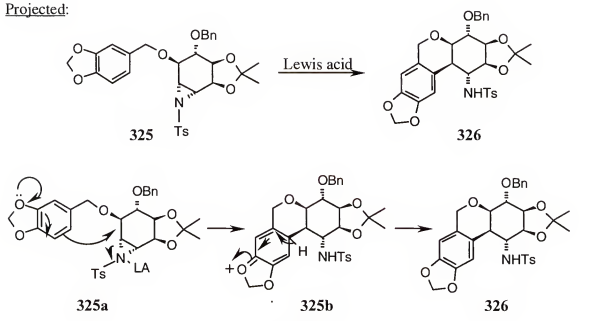


324 327

Scheme 78

cyclialkylations of tethered epoxides[102] in addition to reports of Friedel-Crafts reactions between aromatic systems and activated aziridines.[83-84,86-87] As illustrated in Scheme 79, it was envisioned that closure of the piperonyl moiety through its electron rich pi system onto the postulated aziridine ring could be invoked under acidic conditions. The results

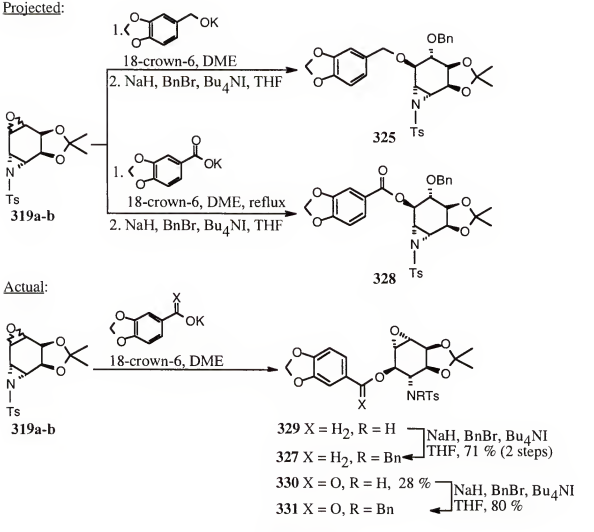
of several investigations of the proposed acid mediated intramolecular cyclization will be discussed in the following section.



Scheme 79

The synthetic route used to prepare the postulated aziridine **325** was also based on earlier reports internal to the research group[107] indicating that nucleophilic attack of the oxirane would be more facile than opening of the aziridine under basic conditions. Presumed selective opening of the epoxide ring upon treatment of the epoxyaziridines **319a-b** with either the potassium salt of piperonol or the potassium salt of piperonylic acid furnished the postulated aziridines **325** and **328** following benzylation as depicted in the projected path, Scheme 80. Initially, examination of the acid mediated closure was studied on the presumed aziridine **325** in which the piperonyl unit is tetherd as an ether since the postulated aziridine **328** contains a more deactivated piperonyl unit tethered as

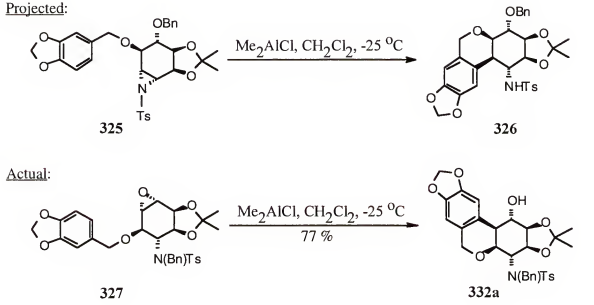
an ester. In actuality, treatment of epoxyaziridines **319a-b** with the potassium salts of piperonol or piperonylic acid resulted in selective attack of the aziridine ring leading to the formation of the tosylamides **327** and **331** following benzylation as shown in the actual sequence, Scheme 80.



Scheme 80

Unfortunately, it was discovered that both piperonyl nucleophiles actually open the aziridine ring within epoxyaziridines **319a-b** under basic conditions only following identification of lactone **353** (Scheme 76) at the end of the synthesis.

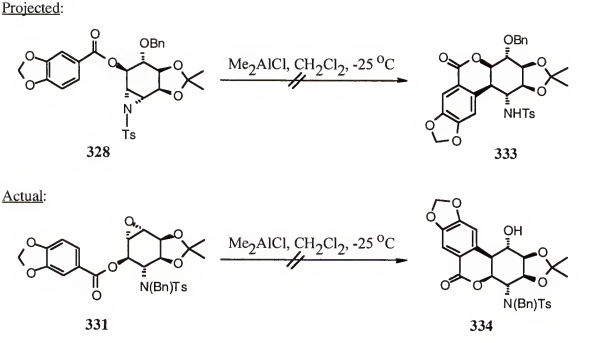
With the presumption that a means of generating aziridine **325** had been established, the acid mediated intramolecular cyclization was attempted using trifluoroacetic acid, boron trifluoride diethyletherate, and alumina, all of which failed to invoke cyclization. However, treatment of the postulated aziridine **325** with dimethylaluminum chloride at –25 °C in methylene chloride successfully invoked intramolecular cyclization giving rise to tosylamide **326** as illustrated in the projected path, Scheme 81.



Scheme 81

It was subsequently determined that Lewis acid mediated intramolecular cyclization of epoxide **327** proceeded to form alcohol **332a** via closure of the electron rich piperonyl moiety onto the oxirane as ahown in the actual sequence, Scheme 81.

The attempted cyclization of the presumed ester **328** using dimethylaluminum chloride as the acid left ester **328** unchanged and failed to generate the corresponding lactone **333** as shown in the projected path, Scheme 82. At this time, it was assumed that the failed cyclization was possibly attributed to the enhanced deactivation of the aryl ring in the postulated aziridine **328** towards electrophilic aromatic substitution. In retrospect, the Lewis acid mediated cyclization of ester **331** was actually attempted and failed to produce lactone **334** as depicted in the actual path, Scheme 82. Nevertheless, the Lewis acid mediated cyclization of ether **327** proceeded well to furnish pentacycle **332a** as mentioned previously and illustrated in Scheme 81.



Scheme 82

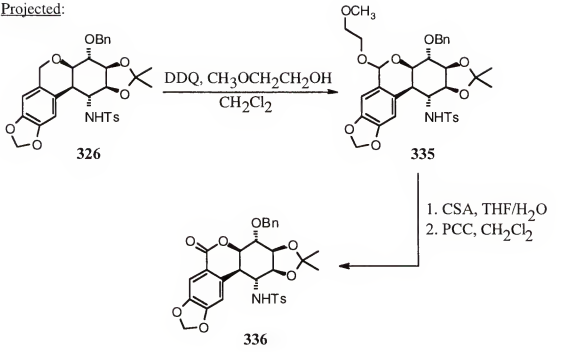
Further Functionalizations of Arylconduramines

While it appeared that the postulated tosylamide **326** was reached, the stage was set to perform additional functionalization which would presumably allow for formation of the lactam functionality present in the alkaloid. Included among such auxiliary functionalizations are the oxidation of the benzylic position present in the benzopyran unit, the removal of the tosyl group, and finally hydrolysis and rearrangement which would provide the skeleton of the natural product.

Benzylic oxidation

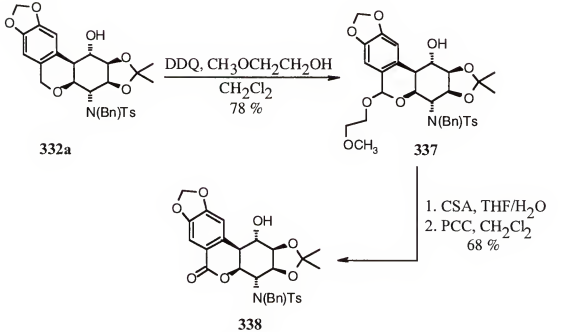
Oxidation of the benzylic position of the benzopyran system present within the postulated tosylamide **326** would allow for the construction of the corresponding lactone which could undergo hydrolysis and concomitant transamidation. Successful oxidation of the benzylic position was found to proceed upon treatment of the presumed tosylamide **326** with DDQ[103] followed by trapping of the intermediate oxonium ion with 2-methoxyethanol furnishing the postulated acetal **335** as shown in the projected path, Scheme 83. Cleavage of the acetal unit with camphorsulfonic acid afforded the lactol which was immediately oxidized with pyridinium chlorochromate to give the presumed lactone **336**. In actuality, benzylic oxidation of the activated benzopyran unit in alcohol **332a** provided acetal **337** which was subsequently converted into lactone **338** via hydrolysis of the acetal group followed by oxidation of the ensuing lactol as illustrated in the actual sequence, Scheme 83. However, it was not until the isolation and identification of tetracetate **353** (Scheme 76) at the end of the synthesis that the actual benzylic oxidation sequence was resolved.

Projected:



326 **335** **336**

Actual:



332a **337** **338**

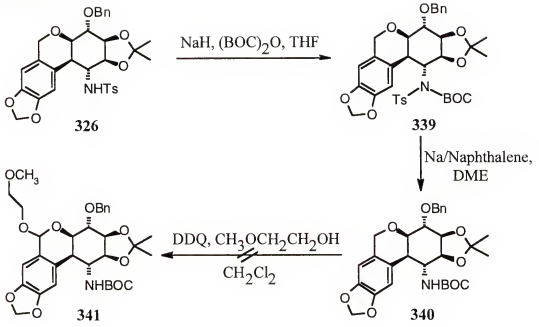
Scheme 83

Detosylation studies

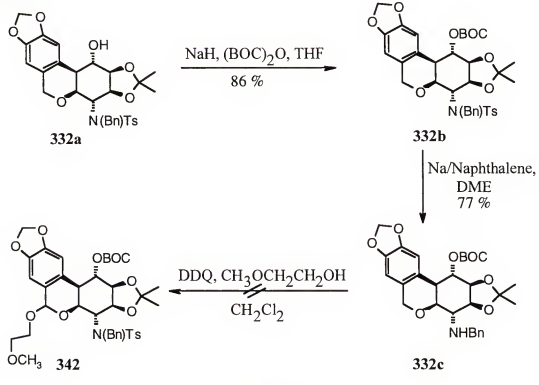
In order to establish the best stage at which to remove the tosyl group in the presumed path to the alkaloid, the deprotection of several sulfonamides generated throughout the proposed synthesis was examined. Acylation of the postulated sulfonamide **326** resulted in generation of the assumed benzopyran **339** as shown in the projected path, Scheme 84. Reductive detosylation occurred smoothly to seemingly produce the *tert*-butyl carbamate **340**; nevertheless, the attempted oxidation of the benzylic position with DDQ and 2-methoxyethanol as descibed previously (Scheme 83) failed to afford the acetal **341**. At this time, the reductive detosylation process appeared to provide a means of preparing *tert*-butyl carbamates which can be easily converted to the corresponding free amines necessary for the transamidation process. In retrospect, acylation of the hydroxyl functionality present in benzopyran **332a** occurred to generate carbonate **332b** which was subsequently transformed into N-benzylamine **332c** under reductive detosylation conditions as illustrated in the actual sequence, Scheme 84. The attempted oxidation of the benzylic position within the activated benzopyran system using DDQ and 2-methoxyethanol was actually performed on N-benzylamine **332c** which failed to produce acetal **342**.

As a result of failure in oxidizing the benzylic position within benzopyran **340**, the detosylation sequence was applied to the presumed sulfonamide **335** (Scheme 83) in which the acetal unit has already been incorporated into the molecule. Following acylation of the postulated acetal **335**, which was presumed to generate the corresponding N-acyl sulfonamide, reductive detosylation was performed supposedly furnishing the acetal **343** as shown in the projected path, Scheme 85.

Projected:

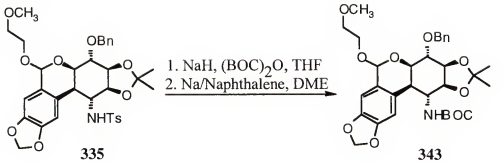


Actual:



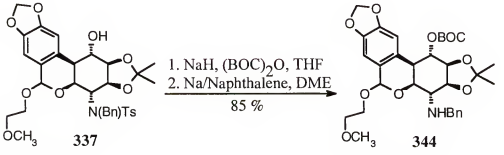
Scheme 84

Projected:



335 343

Actual:



337 344

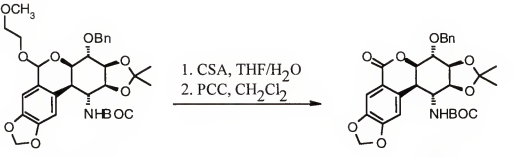
Scheme 85

In actuality, hydroxy acetal **337** was subjected to the acylation conditions to give the corresponding carbonate which upon reductive detosylation furnished N-benzylamine **344** as illustrated in the actual sequence, Scheme 85. Unfortunately, standard spectroscopic techniques failed to adequately distinguish between compounds in the projected and actual paths in the detosylation sequences. It was not until the preparation and identification of tetracetate **353** (Scheme 76) at the conclusion of the synthesis that the actual synthetic transformations performed throughout the detosylation studies were determined.

Final Transformations

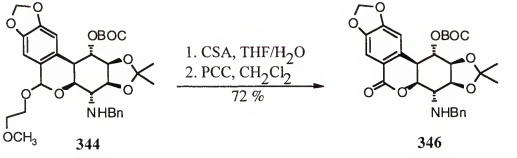
With the methodology developed for generating the postulated acetal **343**, the final transformations, including further oxidation of the acetal functionality, removal of protecting groups, and the transamidation protocol, were performed in the presumed path to the alkaloid. Cleavage of the acetal functionality in the postulated carbamate **343** under acidic conditions furnished the lactol which was immediately converted into the assumed lactone **345** via pyridiniumn chlorochromate mediated oxidation as shown in the projected path, Scheme 86. Unfortunately, it was subsequently discovered that cleavage of acetal **344** followed by oxidation of the crude lactol afforded lactone **346** as illustrated in the actual sequence, Scheme 86.

Projected:



343 **345**

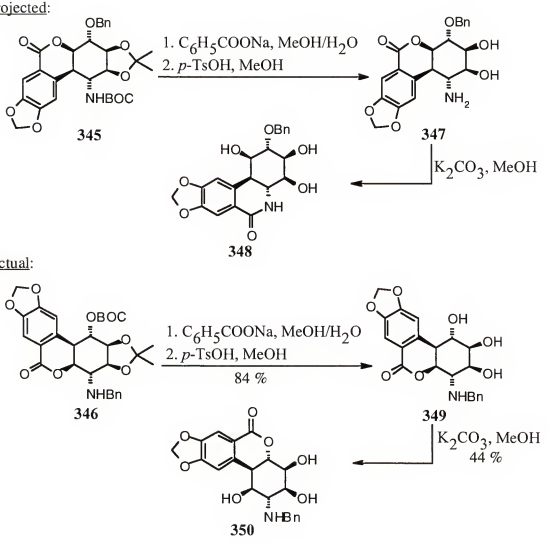
Actual:



344 **346**

Scheme 86

The removal of the protecting groups present in the functionalized cyclohexyl ring of the postulated lactone **345** was examined. First, deprotection of the *tert*-butoxycarbonyl group by thermolysis followed by removal of the acetonide generated the presumed diol **347** as illustrated in the projected path, Scheme 87. Further treatment of the postulated amino diol **347** with potassium carbonate in methanol should have furnished lactam **348** in which the skeleton of the alkaloid would have been constructed.



Scheme 87

In retrospect, deprotection of the carbonate in lactone **346** followed by removal of the acetonide group produced triol **349** which was subsequently transformed into triol **350** via hydrolysis as depicted in the actual sequence, Scheme 87. In addition to the production of *trans*-lactone **350**, the hydrolysis also gave the *cis*-lactone **349**.

Removal of the benzyl group in the postulated lactam **348** (Scheme 87) should have furnished the natural product; however, the conditions utilized for the final debenzylation (H_2, $Pd(OH)_2$, MeOH) did not produce (+)-7-deoxypancratistatin (**6**) based on thin layer chromatography as represented in Figure 8.

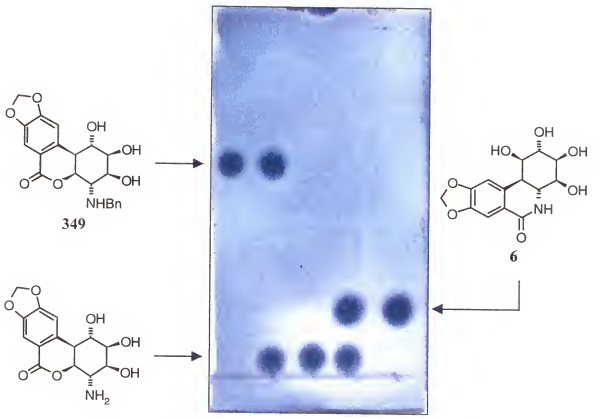
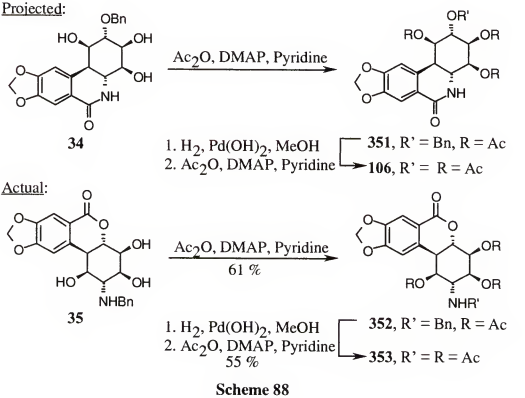


Figure 8. TLC Comparison with (+)-7-deoxypancratistatin

The failure in generating a physical match by thin layer chromatography in combination

with difficulties in purifying the product obtained from the hydrogenation gave the appearance that the debenzylation conditions were ineffective for conversion of the presumed lactam **348** (Scheme 87) to the natural product.

Therefore, an effort to convert the presumed lactam **348** into the tetraacetate of (+)-7-deoxypancratistatin was examined. Acylation of the hydroxyl groups in the postulated lactam **348** appeared to give the triacetate **351** as shown in the projected path, Scheme 88. Removal of the benzyl group by hydrogenation followed by acylation of the resulting alcohol would give the known tetraceate of (+)-7-deoxypancratistatin.[29a,c] Debenzylation of the presumed lactam **351** occurred smoothly to produce what appeared to be the corresponding alcohol which was then subjected to acylation with the hope that the tetracetate of (+)-7-deoxypancratistatin (**106**) would be obtained.



Scheme 88

The sequence involving debenzylation and subsequent acylation ultimately led to the isolation of a compound whose ^{1}H NMR spectrum was remarkably similar to that of the tetracetate of (+)-7-deoxypancratistatin (**106**) yet not identical. In addition, the R_f values in thin layer chromatography did not coincide as represented in Figure 9.

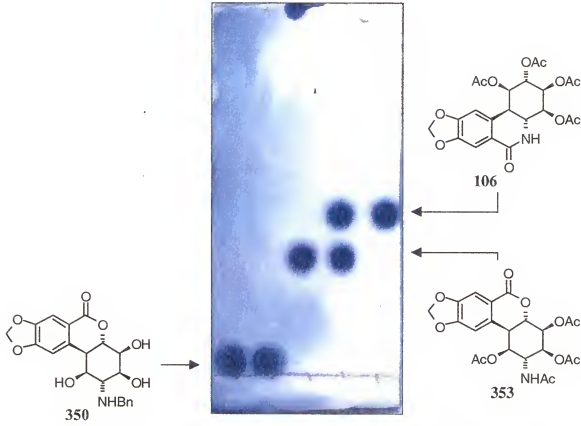


Figure 9. TLC Comparison with the Tetraacetate of (+)-7-deoxypancratistatin

Only at this stage of the synthesis was it discovered that the actual synthetic sequence and the projected path to the alkaloid were not in agreement. In retrospect, triol **350** was converted into triacetate **352** which upon debenzylation and acylation of the resulting free amine gave tetracetate **353** as illustrated in the actual path, Scheme 88.

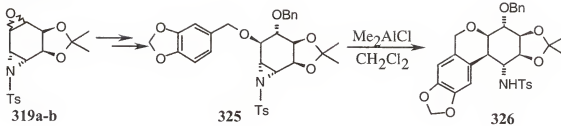
In this synthesis, the functionalized lactone **353** was prepared in 14 steps from the epoxyaziridines **319a-b** in which a Lewis acid mediated intramolecular cyclization served as the key step. Interestingly, the *cis*-lactone **349** did isomerize to the *trans*-lactone **350** (actual sequence, Scheme 87) both of which manifest distinctly different chromatographic and spectral properties.

Unfortunately, standard nuclear magnetic resonance spectroscopic experiments failed to adequately distinguish between aziridine **321** and epoxide **323** in the projected and actual paths respectively (Scheme 77). The ambiguity in the NMR spectra continued to be problematic in discriminating between the projected and actual transformations which were performed throughout the synthesis. Only after discrepancies arose in the comparison of the ^{1}H NMR spectra and R_f values in thin layer chromatography for tetraacetates **353** and **106** (Scheme 88) was it determined that the projected path to the alkaloid did not coincide with the actual synthetic sequence.

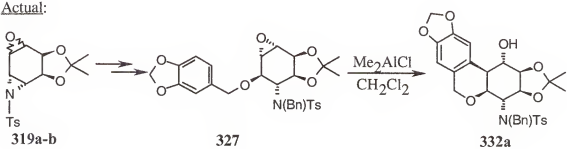
Structure Assignment

As it was clear at this point that the tetraacetate of (+)-7-deoxypancratistatin had not been prepared, several correlational NMR spectroscopic experiments were performed in order to evaluate the structural integrity of the intermediates prepared in the projected path to the alkaloid. The results of a variety of two dimensional NMR experiments discussed below failed to adequately distinguish between the tosylamide **326** of the projected path and alcohol **332a** of the actual sequence as shown in Scheme 89. Ultimately, the unambiguous assignment of alcohol **332a** was made by means of ^{15}N GHMQC spectroscopy described at the end of the following section.

Projected:



Actual:



Scheme 89

In the aromatic region of the proton spectrum of tosylamide **332a**, the two doublets of the tosyl moiety, the overlapping signal from the benzyl group, and the signals of the piperonyl functionality were identified by long range ^{1}H-^{13}C couplings within these fragments as shown in Figure 10.

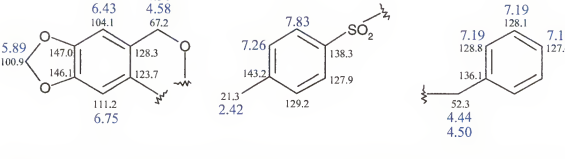


Figure 10. Assignments of the Piperonyl, Tosyl, and Benzyl Moieties in Amide **332a**

From long range ^{1}H-^{13}C coupling experiments, the protons of the methyl groups of the acetonide (1.29 and 1.31 ppm) couple with the carbon at 109.8 ppm which, in turn, exhibits long range coupling with the proton at 4.75 ppm (Figure 11).

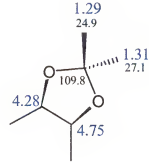


Figure 11. Assignments of the Acetonide Unit of Tosylamide **332a**

As shown in Figure 12, the signal at 1.31 ppm of the methyl group from the acetonide displays an nOe with the protons (4.75 and 4.28 ppm) located at the bridgehead of the cyclohexyl and acetonide rings.

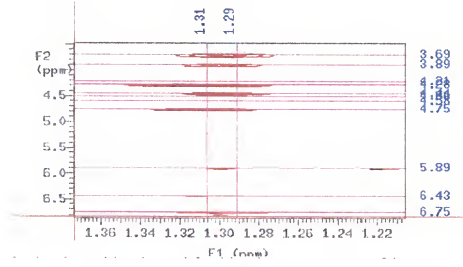


Figure 12. Partial NOESY Spectrum of Amide **332a**

This nOe indicates that the methyl group of the acetonide at 1.31 ppm and the protons of the cyclohexyl ring at 4.28 and 4.75 ppm are in a *cis* relationship relative to one another as illustrated in Figure 11.

The proton signals of the inositol moiety were identified from the DQCOSY spectrum (Figure 13) giving the coupling sequence 4.21-2.47-3.89-4.28-4.75-3.69-4.21 along the functionalized cyclohexyl ring.

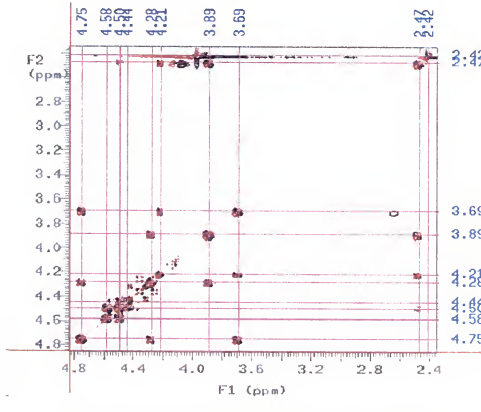


Figure 13. Partial DQCOSY Spectrum of Amide **332a**

The assignment of the carbon atoms was obtained from the GHMQC spectrum and is shown in the complete assignment of the inositol moiety of tosylamide **332a**, Figure 14.

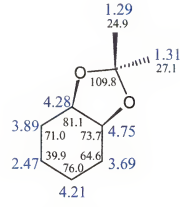


Figure 14. Carbon Hydrogen Framework of the Cyclohexyl Unit of Amide **332a**

Long range ^{1}H-^{13}C coupling in the HETCOR spectrum (Figure 15) between the proton at 6.75 ppm and the carbon atom at 39.9 ppm confirmed the connectivity between the piperonyl species and the inositol unit as illustrated in Figure 16. Additional evidence

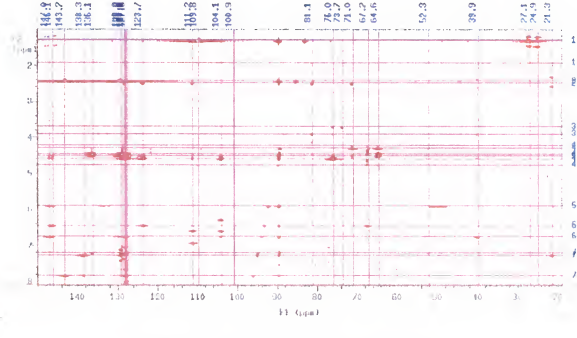


Figure 15. HETCOR Spectrum of Amide **332a**

for the connectivity between the piperonyl moiety and the inositol fragment as shown in Figure 16 arises from long range ^{1}H-^{13}C coupling (HETCOR spectrum, Figure 15) of the protons at 4.50 and 4.58 ppm with carbon atom at 76.0 ppm.

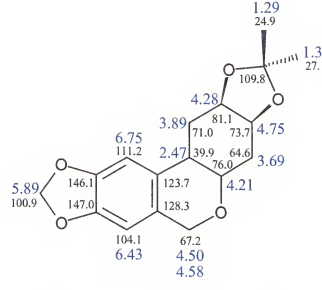


Figure 16. Connectivity of the Piperonyl Unit of Tosylamide **332a**

The location of the benzyl group was also determined from significant long range ^{1}H-^{13}C couplings in the HETCOR spectrum, Figure 15. Long range coupling of the carbon atom at 64.6 ppm with the methylene protons (4.50 and 4.44 ppm) associated with the benzyl functionality confirmed the connectivity between the inositol unit and the benzyl group as illustrated in Figure 17.

Indirect evidence for the location of the tosyl moiety in amide **332a** was obtained through examination of significant nOe's of the tosyl group which are revealed in NOESY spectrum as shown in Figure 18. The proton at 1.92 ppm (Figure 19) is coupled with the proton at 3.89 ppm (DQCOSY) and exchanges with water (NOESY), thus

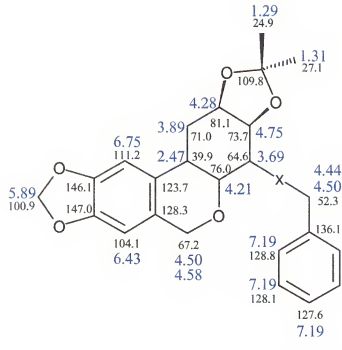


Figure 17. Location of the Benzyl Group of Amide **332a**

confirming that the proton at 1.92 ppm is attached to a heteroatom. While the proton at 1.92 ppm displays expected nOe's with the protons at 6.75, 2.47, 3.89 and 4.28 ppm, no nOe is observed between the proton at 1.92 ppm and the proton at 7.83 ppm of the tosyl functionality (Figure 10).

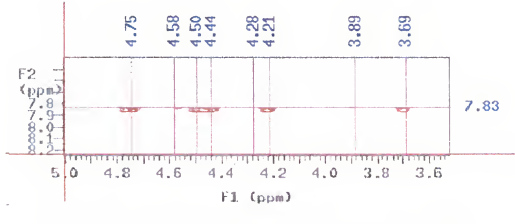


Figure 18. Significant nOE's of the Tosyl Group in Amide **332a**

On the other hand, the proton at 7.83 ppm of the tosyl group displays nOe's with the protons at 3.69, 4.75, 4.21, 4.44 and 4.50 ppm (Figure 18) which suggests that the tosyl functionality is vicinal to the oxygen atom of the benzopyranyl system and adjacent to the benzyl group as shown in the in Figure 19.

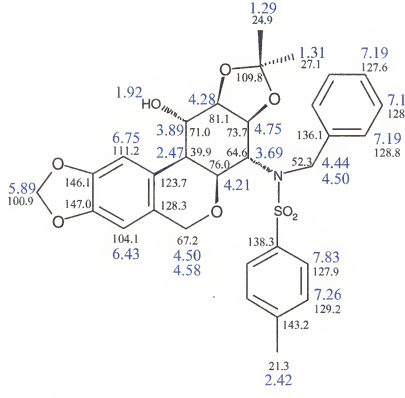


Figure 19. Complete Structural Assignment of Amide **332a**

The nOe's exhibited between the protons of the methyl group of the acetonide at 1.29 ppm and the protons of the inositol unit at 3.69 and 3.89 ppm indicate that all these protons are on the same face of the ring. In addition, all other protons on the inositol ring (2.47, 4.21, 4.28, and 4.75 ppm) display mutual nOe's indicating that these protons are in a *cis* relationship relative to one another as shown in Figure 19. *Unfortunately, the* ^{1}H-^{1}H

*couplings, nOe's, and long range ^{1}H-^{13}C couplings failed to adequately discriminate between between tosylamide **326** and alcohol **332a** of the projected and actual synthetic sequences as shown previously in Scheme 89.*

Absolute proof of the structural integrity of alcohol **332a** as shown below was obtained by ^{15}N nuclear magnetic resonance spectroscopy. Acquisition of the proton spectrum in deuterated toluene at 70 °C gave first order spectra, the proton assignment shown in Figure 20.

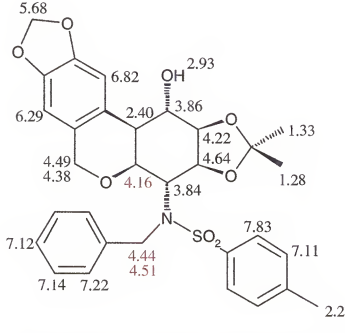


Figure 20. Proton Assignment of Amide **332a**

Long range ^{1}H-^{15}N coupling (Figure 21) between the nitrogen nucleus (277.9 ppm) with the protons of the benzyl group (4.44 and 4.51 ppm) and with the proton of the inositol unit at 4.16 ppm confirmed the connectivity of the tosylamide to the functionalized cyclohexyl ring as illustrated in Figure 20.

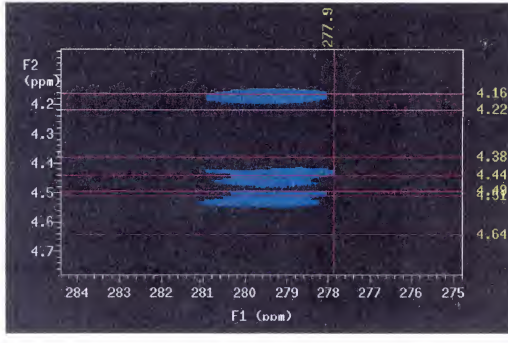
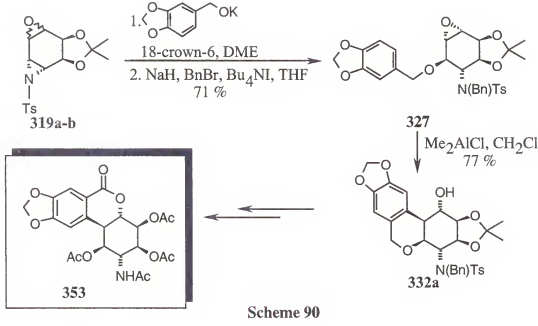


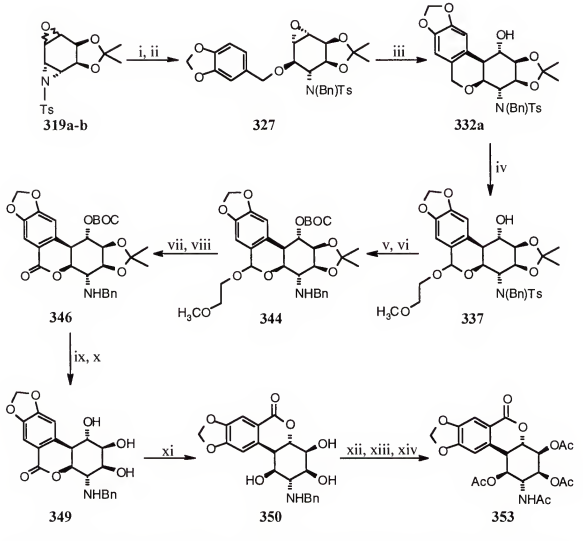
Figure 21. ^{15}N GHMQC Spectrum of Tosylamide **332a**

*Only after acquisition of the ^{15}N GHMQC spectra was the actual synthetic sequence, as depicted in Scheme 90, ascertained and the identification of tetracetate **353** made.*



Scheme 90

In summary, tetraacetate **353** was prepared in 14 steps and in 3.3 % overall yield starting from the mixture of α and β epoxyaziridines **319a-b** as depicetd in Scheme 91.

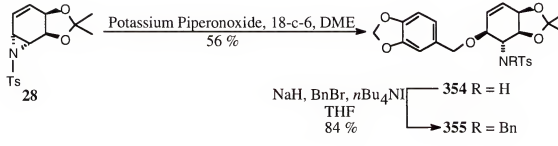


i. Potassium Piperonoxide, DME, 18-crown-6; ii. NaH, BnBr, *n*-Bu_4NI, THF 71 % (over 2 steps); iii. Me_2AlCl, CH_2Cl_2, -25 °C, 77 %; iv. DDQ, 2-methoxyethanol, CH_2Cl_2, 78 %; v. NaH, $(BOC)_2O$, THF; vi. Na/Naphthalene, DME, -50 °C, 85 % (over 2 steps); vii. CSA, THF/H_2O; viii. PCC, CH_2Cl_2, 72 % (over 2 steps); ix. $C_6H_5CO_2Na$, MeOH/H_2O, reflux; x. *p*-TsOH, MeOH, 84 % (over 2 steps); xi. K_2CO_3, MeOH, reflux, 44 %; xii. Ac_2O, pyridine, DMAP, 61 %; xiii. H_2, $Pd(OH)_2$, MeOH; xiv. Ac_2O, pyridine, DMAP, 55 % (over 2 steps)

Scheme 91

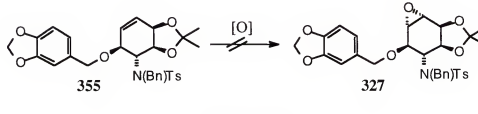
Structure Correlation by Independent Synthesis

In addition to the spectroscopic evidence for the structure of alcohol **332a**, the synthetic sequence as depicted in Scheme 90 was proved through a structure correlation. As shown in Scheme 92, treatment of vinylaziridine **28** with the potassium salt of piperonol in 1,2-dimethoxyethane furnished tosylamide **354** which was converted into sulfonamide **355** upon benzylation.



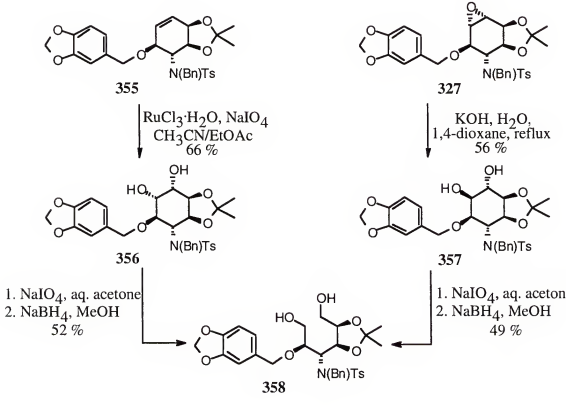
Scheme 92

With tosylamide **355** in hand, a stereoselective epoxidation of the olefin, if successful, would give epoxide **327** (Scheme 90) and provide the structure correlation. Unfortunately, several attempts to oxidize the olefin with an array of epoxidizing agents, including *m*CPBA, dimethyldioxirane, and many hydrogen peroxide derived oxidants, failed to generate epoxide **327** as depicted in Scheme 93.



Scheme 93

Successful oxidation of N-benzyl tosylamide **355** with ruthenium tetroxide[95] gave *cis* diol **356**; moreover, stereoselective opening of the epoxide ring in tosylamide **327** with hydroxide furnished *trans* diol **357** as shown in Scheme 94. It was envisioned that the two stereisomeric diols **356** and **357** could be converted into a common intermediate via oxidative degradation of the diol moiety followed by reduction of the crude dialdehyde. Treatment of both diol **356** and **357** with sodium periodate resulted in cleavage of the diol unit generating the corresponding dialdehydes. Interestingly, cleavage of *cis* diol **356** proceeded at a rate five times faster than that for *trans* diol **357**. Reduction of the crude dialdehydes generated from oxidative degradation of diols **356** and **357** gave diol **358** (Scheme 94).

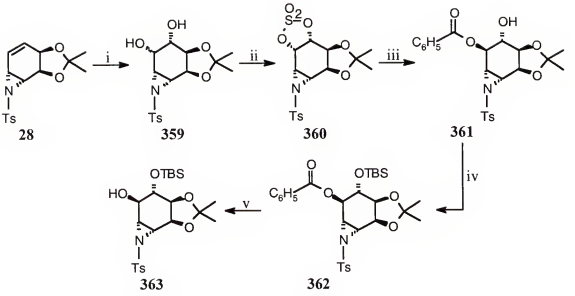


Scheme 94

The spectral and physical properties (^{1}H NMR, $[\alpha]_D$, TLC, IR) of diol **358**, prepared indepedently from both vinylaziridine **28** and epoxyaziridines **319a-b**, were identical in all respects thus proving the synthetic sequence shown in Scheme 90 via correlation.

Correction of the Design of Aryl Ether Precursor of Type **325**

Since it was discovered that piperonyl nucleophiles selectively attack the aziridine ring in epoxyaziridines **319a-b** under basic conditions, a modified approach to the synthesis of (+)-7-deoxpancratistatin (**6**) was examined. Stereoselective dihydroxylation of vivnylaziridine **28** with ruthenium tetroxide[95] generated diol **359** which was subsequently converted into cyclic sulfate **360** by established procedures[108] as shown in Scheme 95. It was envisioned that nucleophilic attack on the sulfate could proceed without detriment to the aziridine based on reported openings of cyclic sulfates by the ammonium salts of carboxylic acids.[109] Treatment of sulfate **360** with ammonium benzoate resulted in a regioselective and stereoselective attack of the cyclic sulfate furnishing alcohol **361** following sulfate hydrolysis. Protection of the hydroxyl functionality as the silyl ether afforded benzoate **362** which was transformed into alcohol **363** via hydrolysis of the ester.



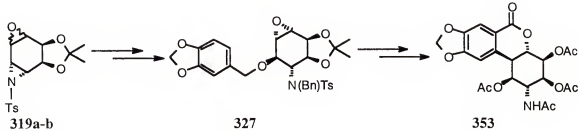
i. $RuCl_3 3H_2O$, $NaIO_4$, EtOAc/CH_3CN, 45 %; ii. SO_2Cl_2, Et_3N, CH_2Cl_2; iii. (a) Ammonium benzoate, DMF, 70 °C; (b) H_2SO_4, H_2O, THF; 51 % (over 3 steps); iv. TBSCl, imidazole, CH_2Cl_2, 81 %; v. NaOMe, THF/MeOH, 48 %.

Scheme 95

CHAPTER 4
CONCLUSIONS AND FUTURE WORK

Conclusions

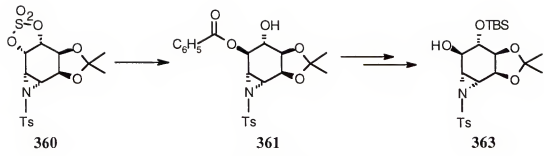
Clearly, the synthetic route to the synthesis of (+)-7-deoxypancratistatin (**6**) via epoxyaziridines **319a-b** is plagued by the unexpected opening of the aziridine ring rather than the oxirane by piperonyl nucleophiles under basic conditions. Unfortunately, the selective opening of the aziridine ring by piperonyl reagents was only determined with the identification of tetraacetate **353** at the conclusion of the synthesis as shown in Scheme 96.



319a-b **327** **353**

Scheme 96

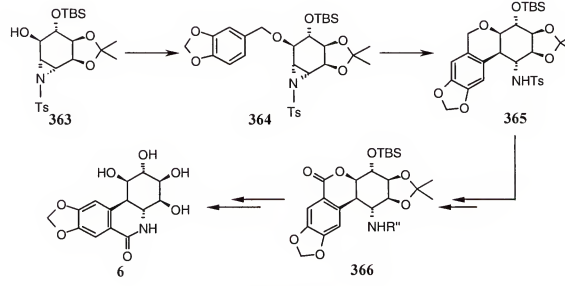
However, in the corrected approach, nucleophilic opening of cyclic sulfate **360** with ammonium benzoate occurs with retention of the aziridine ring affording alcohol **361** which can be converted into aziridine **363** in a two step sequence shown in Scheme 97.



Scheme 97

Future Work

The key steps which remain in the approach to the synthesis of (+)-7-deoxypancratistatin (**6**) include alkylation of alcohol **363** with piperonyl bromide which would furnish ether **364**. Lewis acid mediated intramolecular cyclization would give benzopyran **365** which could be converted to lactone **366** via the methodology employed in the synthesis of tetraaceate **353**. Hydrolysis of lactone **366** followed by transamidation would ultimately lead to the preparation of the alkaloid as illustrated in Scheme 98.



Scheme 98

CHAPTER 5
EXPERIMENTAL

General Procedures and Instrumentation

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried under vacuum. Tetrahydrofuran and 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. Reactions were monitored by thin layer chromatography using K6F silica gel (Whatman) plates. Flash column chromatography was performed on Merck silica gel (grade 60, 230-400 mesh). Melting points were determined on a Thomas Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer 1600 Series FT-IR spectrometer. High resolution mass spectra were measured on a Sinnigan Mat 95Q mass spectrometer. Nuclear magnetic resonance spectra were recorded on either a Varian Unity-300, Gemini 300, or Inova 500 FT-NMR spectrometer in $CDCl_3$ unless otherwise noted. Coupling constants are measured in hertz and chemical shifts are reported in ppm downfield from trimethyl silane. Optical rotations were measured on a Perkin Elmer model 341 polarimeter.

Experimental Procedures and Data

N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-dihydroxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]-4'-methylbenzenesulfonamide (**309**)

A solution of sulfonamide **308** (2.30 g, 5.19 mmol) in a 1:1 mixture of CH_3CN/EtOAc (65 mL) at 0 °C was treated with a solution of $RuCl_3 H_2O$ (81 mg, 0.39 mmol) and $NaIO_4$ (1.66 g, 7.76 mmol) in H_2O (11 mL) and stirred at 0 °C for 3 minutes. The reaction was subsequently quenched with a 50 % aqueous solution of $Na_2S_2O_3$ (100 mL) and then warmed to room temperature. The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 2:1 ethyl acetate/hexanes) to afford diol **309** (1.87 g, 75 %) as a white solid: R_f 0.14 (2:1 hexanes/ethyl acetate); m.p.: 103-105 ° C; $[\alpha]^{29}_D$ –27.1 (*c* 1.0, CH_3OH); IR (KBr) ν 3482, 1599, 1490, 1246, 1159, 1036 cm^{-1}; ^1H NMR (500 MHz, acetone) δ 7.49 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.59 (d, J = 1.7 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.52 (dd, J = 8.0, 1.6 Hz, 1H), 6.34 (d, J =9.6 Hz, 1H), 5.94 (m, 2H), 4.51 (m, 1H), 4.32 (dd, J = 5.9, 2.9 Hz, 1H), 4.21 (t, J = 6.1 Hz, 1H), 4.02 (m, 1H), 3.94 (ddd, J = 8.5, 6.0 Hz, 1H), 3.77 (td, J = 8.8, 6.3 Hz, 1H), 3.67 (d, J = 5.8 Hz, 1H), 2.83 (t, J = 8.8 Hz, 1H), 2.40 (s, 3H), 1.49 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 145.8, 142.1, 137.4, 132.6, 128.5, 126.1, 121.4, 108.4, 107.5, 100.2, 76.5, 75.9, 71.0, 69.7, 56.7, 49.4, 26.4, 24.3, 20.7; HRMS (FAB) calcd for $C_{23}H_{28}NO_8S$ 478.1536, found 478.1516; Anal. Calcd for $C_{23}H_{27}NO_8S$: C, 57.85; H, 5.70; N, 2.93. Found: C, 57.76; H, 5.79; N, 2.83.

N-[((1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(hydroxymethyl))propyl]-4'-methylbenzenesulfonamide (**310**)

A solution of diol **309** (1.72 g, 3.60 mmol) in a 4:1:1 mixture of THF/H_2O/TFA (30 mL) was stirred at room temperature for 17 hours. After removal of the solvents by Kügelrohr distillation, the residue was dissolved in a 3:2 mixture of acetone/H_2O (30 mL) and subsequently treated with a solution of $NaIO_4$ (2.13 g, 9.97 mmol) in H_2O (13 mL). The resulting solution was stirred at room temperature for 4 hours and then diluted with water (5 mL). Excess acetone was removed under reduced pressure, and the remaining solution was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and then concentrated *in vacuo*. A solution of the remaining residue in CH_3OH (120 mL) at 0 °C was treated with $NaBH_4$ (1.60 g, 42.3 mmol) and then slowly warmed to room temperature. After stirring for a period of 14 hours, the solution was diluted with H_2O (20 mL) and excess methanol removed under reduced pressure. The resulting solution was extracted with ethyl acetate (2 x 60 mL), and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, 3:2 CH_2Cl_2/acetone) gave tosylamide **310** (820 mg, 60 %) as a white solid: R_f 0.61 (1:1 CH_2Cl_2/acetone); m.p.: 137-139 °C; $[\alpha]^{25}_D$ +50.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3464, 3303, 1501, 1440, 1334, 1156, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 7.8 Hz, 1H), 6.61-6.58 (m, 2H), 5.94 (s, 2H), 4.90 (d, J = 8.4 Hz, 1H), 3.95 (t, J = 9.9 Hz, 1H), 3.71-3.59 (m, 2H), 3.53-3.40 (m, 2H), 3.16 (bs, 1H), 2.92 (dt, J = 8.6, 5, Hz, 1H), 2.63 (bs, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 146.8, 143.5, 137.0, 131.6, 129.6, 126.9, 121.6, 108.5, 108.4, 101.0, 62.9, 62.8, 55.9, 48.8, 21.5;

HRMS (CI) calcd for $C_{18}H_{22}NO_6S$ 380.1168, found 380.1166; Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.83; H, 5.52; N, 3.66.

N-(*tert*-butoxycarbonyl)-N-[((1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-(*tert*-butoxycarbonyloxy)-1-(hydroxymethyl))propyl]-4'-methylbenzenesulfonamide (**314**)

To a suspesion of NaH (87.0 mg, 3.63 mmol) in THF (7 mL) at 0 °C was added a solution of diol **310** (425 mg, 1.12 mmol) in THF (7 mL), and the resulting solution was stirred at 0 °C for 20 minutes. A solution of di-*tert*-butyl dicarbonate (783 mg, 3.58 mmol) in THF (5 mL) was added dropwise and the solution was allowed to slowly warm to room temperature. After stirring for 20 hours, the reaction was quenched with H_2O, and the reaction mixture was then extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The remaining residue was purified via chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford alcohol **314** (552 mg, 85 %) as a white solid: R_f 0.62 (1:1 hexanes/ethyl acetate); m.p. 67-69 °C; $[\alpha]^{25}_D$ +18.1 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3284, 1744, 1492, 1252, 1160, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 HZ, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.68 (d, J =7.7 Hz, 1H); 6.55-6.56 (m, 2H), 5.90 (s, 2H), 4.52 (bs, 1H), 4.21 (dd, J = 11.0, 7.6 Hz, 1H), 4.15 (dd, J = 11.0, 6.0 Hz, 1H), 3.93-3.81 (m, 3H); 3.13 (dd, J = 10.7, 7.1 Hz, 1H); 2.40 (s, 3H); 1.42 (s, 18 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 168.6, 168.5, 153.0, 152.8, 147.8, 147.1, 143.3, 137.3, 129.5, 129.4, 127.0, 121.9, 108.7, 108.4, 101.0, 82.5, 82.1, 66.3, 66.1, 52.6, 44.8, 27.6, 27.5, 21.5; HRMS (EI) calc for $C_{28}H_{37}NO_{10}S$ 579.2138, found 579.2128; Anal. Calcd for $C_{28}H_{37}NO_{10}S$: C, 58.02; H, 6.43; N, 2.42. Found: C, 57.75; H, 6.43; N, 2.33.

Methyl N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-dihydroxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]carbamate (**316**)

A solution of $RuCl_3 H_2O$ (81 mg, 0.39 mmol) and $NaIO_4$ (1.65 g, 7.71 mmol) in H_2O (10 mL) was added to a solution of carbamate **315** (1.79 g, 5.14 mmol) in a 1:1 mixture of CH_3CN/EtOAc (50 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 minutes and then quenched with 50 % aqueous $Na_2S_2O_3$ solution (50 ml). After separation of the organic and aqueous layers, the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (silica gel, 4:1 ethyl acetate/hexanes) to furnish diol **316** (1.35 g, 69 %) as a white solid: R_f 0.27 (4:1 ethyl acetate/hexanes); m.p.: 115-117 °C; $[\alpha]^{29}_D$ –47.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3398, 1702, 1508, 1491, 1248, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (m, 2H), 6.70 (dd, J = 8.2, 1.4 Hz, 1H), 5.96 (s, 2H), 4.64 (bs, 1H), 4.37 (dd, J = 5.3, 2.7 Hz, 1H), 4.34 (q, J = 2.3 Hz, 1H), 4.19 (m, 1H), 4.02 (dt, J =10.2, 2.9 Hz, 1H), 3.90 (q, J = 9.7 Hz, 1H), 3.53 (s, 3H), 2.95 (t, J = 9.5 Hz, 1H), 2.76 (m, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.39 (s, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 156.5, 148.0, 146.9, 131.8, 122.2, 109.2, 108.6, 108.4, 101.0, 77.3, 76.7, 72.3, 69.5, 55.5, 52.0, 47.9, 27.8, 25.8; HRMS (FAB) calcd for $C_{18}H_{24}NO_8$ 383.1502, found 383.1500; Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.42; H, 6.18; N, 3.53.

Methyl N-[(1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(hydroxymethyl)propyl] carbamate (**317**)

A solution of diol **316** (1.97 g, 5.17 mmol) in a 4:1:1 mixture of THF/H_2O/TFA (45 mL) was stirred at room temperature for 16 hours. Removal of the solvents via Kügelrohr distillation afforded a residue which was dissolved in a 3:2 mixture of acetone/H_2O (40

mL) and subsequently treated with a solution of $NaIO_4$ (3.73 g, 17.4 mmol) in H_2O (20 mL). After stirring at room temperature for 4 hours, the solution was diluted with H_2O (5 mL) and excess acetone removed under reduced pressure. The remaining solution was extracted with ethyl acetate (3 x 60 mL), dried over Na_2SO_4, and concentrated *in vacuo*. A solution of the residue in CH_3OH (175 mL) at 0 °C was treated with $NaBH_4$ (2.43 g, 64.2 mmol) and then slowly warmed to room temperature over a period of 20 hours. The solution was diluted with H_2O (25 mL) and excess methanol was removed under reduced pressure. The remaining solution was extracted with ethyl acetate (2 x 70 mL) and then dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, 3:2 CH_2Cl_2/acetone) provided carbamate **317** (654 mg, 45 %) as a film: R_f 0.36 (3:2 CH_2Cl_2/acetone); $[\alpha]^{26}_D$ –55.2 (*c* 1.0, $CHCl_3$); IR (neat) ν 3392, 1694, 1505, 1488, 1249, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 1.1 Hz, 1H), 6.64 (dd, J = 8.0, 1.5 Hz, 1H), 5.95 (s, 2H), 5.02 (d, J = 9.1 Hz, 1H), 4.16 (sx, J = 4.7 Hz, 1H), 3.82 (t, J = 4.8 Hz, 1H), 3.75 (m, 1H), 3.71 (s, 3H), 3.68-3.61 (m, 2H), 3.55 (dd, J = 11.6, 5.4 Hz, 1H), 3.03 (dt, J = 9.6, 2.5 Hz, 1H), 2.19 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.8, 146.7, 131.8, 121.6, 108.7, 108.4, 101.0, 63.4, 63.0, 52.9, 52.5, 48.8; HRMS (FAB) calcd for $C_{13}H_{18}NO_6$ 284.1134, found 284.1138; Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05. Found: C, 54.96; H, 5.99.

(2*R*,3*R*)-2-amino-3-(1,3-Benzodioxol-5-yl)-1,4-dihydroxybutane hydrochloride (**318**)

To a solution of diol **317** (198 mg, 0.700 mmol) in CH_3OH (6 mL) was added a solution of 10 % aqueous KOH (4.5 mL), and the resulting solution was heated at reflux for 14 hours. The reaction was allowed to cool to room temperature, and the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried

over Na_2SO_4 and concentrated *in vacuo*. A solution of the remaining residue in CH_3OH (5 mL) was added to a saturated HCl solution in CH_3OH at 0 °C. After allowing the resulting solution to stir for 5 minutes, the solvent was removed under reduced pressure. The residue was dissolved in isopropanol and filtered into chilled diethyl ether. The resulting precipitate was collected by filtration to give amine hydrochloride **318** (149 mg, 82 %) as a pale beige solid: $[\alpha]^{25}{}_D$ +59.0 (*c* 1.0, CH_3OH); IR (neat) ν 3416, 1504, 1490, 1250, 1040 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.79 (s, 1H), 6.73 (m, 2H), 5.86 (s, 2H), 4.24 (t, J = 8.6 Hz, 1H), 4.13 (dd, J = 10.4, 6.3 Hz, 1H), 3.85-3.78 (m, 2H), 3.66 (dd, J = 9.1, 7.4 Hz, 1H), 3.31 (td, J = 7.4, 4.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ149.8, 148.6, 133.7, 122.1, 109.5, 108.7, 102.6, 75.8, 72.2, 59.8, 51.5; HRMS (CI) calcd for $C_{11}H_{16}NO_4$ (M+H-Cl) 226.1079, found 226.1082.

(1*S*,2*S*,4*R*,5*S*,6*S*,7*S*)-5,6-(isopropylidenedioxy)-3-(4'-methylphenylsulfonyl)-8-oxa-3-aza-tricyclo[5.1.0.0]octane (**319a**)

(1*R*,2*S*,4*R*,5*S*,6*S*,7*R*)-5,6-(isopropylidenedioxy)-3-(4'-methylphenylsulfonyl)-8-oxa-3-aza-tricyclo[5.1.0.0]octane (**319b**)

To a degassed solution of aziridine **28** (2.18g, 6.79 mmol) in 1,2-dichloroethane (70 mL) was added *m*CPBA (8.37g, 70 % reagent, 34.0 mmol) along with 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (1.21g, 3.40 mmol) as a radical inhibitor. The resulting solution was heated at reflux for 12 hours. After allowing the solution to cool to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHSO_3$ followed by saturated $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The remainder was purified by chromatography (10 % deactivated silica gel, 4:1 hexanes/ethyl acetate) to give a mixture of epoxyaziridines **319a-b** (1.83g, 80%) as a white solid: R_f 0.43 (2:1 hexanes/ethyl

acetate); m.p.: 107-108 °C; $[\alpha]^{28}_{D}$ –56.5 (*c* 0.8, $CHCl_3$); IR (neat) ν 3000, 1595, 1330, 1255, 1158, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.36 (d, J = 5.7 Hz, 1H), 4.24 (d, J = 6.3 Hz, 1H), 3.53 (t, J = 3.6 Hz, 1H), 3.37 (dd, J = 6.8, 3.8 Hz, 1H), 3.12 (dd, J = 3.3, 1.2 Hz, 1H), 3.03 (dd, J = 6.9, 1.2 Hz, 1H), 2.45 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 134.1, 129.6, 127.7, 109.9, 70.6, 69.5, 49.9, 46.5, 37.1, 35.4, 27.2, 25.0, 21.5; HRMS (FAB) calcd for $C_{16}H_{20}NO_5S$ 338.1062, found 338.1061; Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.97; H, 5.68; N, 4.56. Found: C, 57.37; H, 5.96; N, 3.72.

N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(6'-bromobenzo[1,3]dioxolo-5-ylmethoxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo[4.1.0]hept-3-yl]-4'-methylbenzenesulfonamide (**323**)

To a suspension of KH (21 mg, 0.52 mmol) in DME (3 mL) was added a solution of 6-bromopiperonol (121 mg, 0.524 mmol) in DME (1 mL), and the resulting mixture was stirred for 20 minutes. A solution of epoxyaziridines **319a-b** (35 mg, 0.15 mmol) in DME (0.5 mL) was added dropwise followed by the addition of a catalytic amount of 18-crown-6. The resulting solution was stirred for 15 hours. The reaction was quenched with saturated NH_4Cl solution, and the reaction mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by chromatography (silica gel, 5:1 hexanes/ethyl acetate) to give tosylamide **323** (118 mg, 56%) as a colorless oil: R_f 0.35 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{27}$ +30.9 (*c* 1.0, $CHCl_3$); IR (neat) ν 3500, 3332, 1504, 1480, 1334, 1248, 1090, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.95 (s, 1H), 6.87 (s, 1H), 5.95 (m, 2H), 5.11 (d, J = 10.5 Hz, 1H), 4.52 (dd, J = 6.3, 1.1 Hz, 1H), 4.35 (dd, J = 12.5, 0.5 Hz, 1H), 4.24 (ddt, J = 6.3,

3.4, 1.0 Hz, 1H), 4.16 (dd, J = 12.4, 0.5 Hz, 1H), 3.86 (ddd, J = 10.5, 2.9, 0.9 Hz, 1H), 3.55 (t, J = 2.4 Hz, 1H), 3.29 (ddt, J = 3.6, 2.5, 1.1 Hz, 1H), 3.22 (dt, J = 3.5, 1.2 Hz, 1H), 2.42 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.5, 143.8, 137.6, 130.0, 127.1, 112.6, 112.4, 109.9, 109.0, 101.7, 73.7, 73.3, 71.3, 69.3, 52.8, 52.6, 47.6, 27.0, 24.9, 21.5; HRMS (CI) calcd for $C_{24}H_{27}NO_8SBr$ 568.0641, found 568.0636.

N-Benzyl-N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(6'-bromobenzo[1,3]dioxolo-5-ylmethoxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo[4.1.0]hept-3-yl]-4'-methylbenzenesulfonamide (**324**)

A suspension of NaH (68.4 mg, 60 % reagent, 1.71mmol) in THF (10 mL) was treated with a solution of tosylamide **323** (971 mg, 1.71 mmol) in THF (10 mL) and stirred for 20 minutes after which benzyl bromide (251 μL, 2.07 mmol) was added dropwise followed by the addition of a catalytic amount of tetrabutylammonium iodide. The resulting solution was stirred for 40 hours and then quenched with water. The organic and aqueous layers were separated and the aqueous phase was extracted with ethyl acetate (4 x 45 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The remainder was purified by chromatography (silica gel, 5:1 hexanes/ethyl acetate) to give tosylamide **324** (1.02 g, 90 %) as a pale beige solid: R_f 0.49 (3:1 hexanes/ethyl acetate); m.p. 67-70 °C; $[\alpha]_D^{27}$ –9.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν 1500, 1481, 1331, 1250, 1158, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.19-7.13 (m, 8 H), 7.02 (s, 1H), 6.02 (m, 2H), 4.63-4.56 (m, 2H), 4.30-4.18 (m, 4H), 3.38 (m, 2H), 2.39 (s, 3H), 1.45-1.36 (m , 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.5, 142.9, 138.1, 136.3, 130.0, 129.1, 128.8, 128.4, 128.2, 127.8, 112.8, 112.2, 110.1,

109.9, 101.7, 72.7, 70.6, 57.1, 52.1, 27.3, 25.5, 21.5; HRMS (FAB) calcd for $C_{31}H_{33}NO_8SBr$ 658.1110, found 658.1126.

N-Benzyl-N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(Benzo[1,3]dioxolo-5-ylmethoxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo[4.1.0]hept-3-yl]-4'-methylbenzenesulfonamide (**327**)

To a suspension of KH (757 mg, 0.0189 mmol) in DME (12 mL) was added a solution of piperonol (2.51 g, 16.5 mmol) in DME (7 mL), and the resulting solution was stirred for 20 minutes. A solution of epoxyaziridines **319a-b** (1.59 g, 4.72 mmol) in DME (8 mL) was added dropwise followed by the addition of 18-crown-6 (436 mg, 1.65 mmol). The resulting solution was stirred for 20 hours. The reaction was quenched with saturated NH_4Cl solution and the reaction mixture was extracted with CH_2Cl_2 (4 x 75 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the remaining residue in THF (35 mL) was added dropwise to a suspension of NaH (841 mg, 60 % reagent, 35.0 mmol) in THF (35 mL). The resulting solution was stirred for 20 minutes, and then benzyl bromide (4.30 mL, 36.2 mmol) was added followed by a catalytic amount of tetrabutylammonium iodide. The solution was stirred for 44 hours and then quenched with water. The reaction mixture was extracted with ethyl acetate (4 x 60 mL), and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, 5:1 hexanes/ethyl acetate) to provide epoxide **327** (1.40 g, 71 %) as a white solid: R_f 0.27 (3:1 hexanes/ethyl acetate); m.p. 63-65 °C; $[\alpha]^{26}_D$ –6.9 (*c* 1.0, $CHCl_3$); IR (KBr) ν 2987, 1492, 1445, 1251, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.18-7.10 (m, 7H), 6.81-6.79 (m, 3H), 5.99 (s, 2H), 4.54-4.48 (m, 2H), 4.31-4.26 (m, 2H), 4.16-4.04 (m, 3H), 3.38 (d, J = 3.3 Hz, 1H), 3.30 (d, J = 3.0 Hz, 1H), 2.40 (s, 3H),

1.46-1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.4, 142.8, 138.0, 136.4, 130.9, 129.0, 128.7, 128.3, 128.2, 127.6, 122.1, 110.1, 109.2, 108.0, 101.0, 72.7, 71.3, 57.2, 52.1, 27.3, 25.6, 21.5; HRMS (FAB) calcd for $C_{31}H_{34}NO_8S$ 580.2005, found 580.2050; Anal. Calcd for $C_{31}H_{33}NO_8S$: C, 64.23; H, 5.74; N, 2.42. Found: C, 64.51; H, 5.93, N, 2.28.

N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(Benzo[1,3]dioxolo-5-carbonyloxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo[4.1.0]hept-3-yl]-4'-methylbenzenesulfonamide (**330**)

To a refluxing suspension of potassium piperonylate (2.0 g, 9.8 mmol) and 18-crown-6 in DME (25 mL) was added a solution of epoxyaziridines **319a-b** (801 mg, 2.49 mmol) in DME (10 mL) over a period of 12 hours. The reaction was stirred at reflux for an additional 6 hours. The reaction was quenched with water, and the reaction mixture was extracted with ethyl acetate (4 x 75 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, 3:1 hexanes/ethyl acetate) to provide tosylamide **330** (343 mg, 28 %) as an oil: R_f 0.34 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{26}$ +41.6 (*c* 1.0, $CHCl_3$); IR (neat) ν 3300, 1718, 1508, 1490, 1260, 1161, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 2H), 7.64 (dd, J = 8.2, 1.5 Hz, 1H), 7.44 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.27 (s, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.05 (s, 2H), 5.17 (d, J = 10.4 Hz, 1H), 5.07 (s, 1H), 4.58 (d, J = 6.1 Hz, 1H), 4.31 (m, 1H), 4.03 (dd, J = 10.7, 2.8 Hz, 1H), 3.42 (m, 1H), 3.27 (m, 1H), 2.43 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 152.1, 147.7, 143.7, 137.7, 129.8, 126.9, 125.9, 123.1, 109.9, 109.7, 108.0, 101.9, 73.5, 69.2, 66.5, 52.6, 52.1, 49.1, 27.4, 25.0, 21.5; HRMS (FAB) calcd for $C_{24}H_{26}NO_9S$ 504.1328, found 504.1326.

N-Benzyl-N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(Benzo[1,3]dioxolo-5-carbonyloxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo[4.1.0]hept-3-yl]-4'-methylbenzenesulfonamide (**331**)

To a suspension of NaH (7.2 mg, 60 % reagent, 0.18 mmol) in THF (1 mL) was added a solution of tosylamide **330** (91 mg, 0.81 mmol) in THF (1 mL). The resulting solution was stirred for 20 minutes after which benzyl bromide (33 μL, 0.27 mmol) was added dropwise followed by a catalytic amount of tetrabutylammonium iodide. The reaction was stirred for 48 hours and then quenched with water. The organic and aqueous phases were separated and, the aqueous phase was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 5:1 hexanes/ethyl acetate) to give tosylamide **331** (86 mg, 80 %) as an oil: R_f 0.44 (3:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +19.7 (*c* 1.0, $CHCl_3$); IR (neat) ν 1718, 1491, 1260, 1160, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.65 (s, 1H), 7.17-7.07 (m, 7H), 6.91 (d, J = 8.4 Hz, 1H), 6.07 (s, 2H), 4.64-4.47 (m, 3H), 4.32 (ABq, J = 15. 9 Hz, 2H), 4.10 (m, 1H), 3.42 (d, J =3.0 Hz, 1H), 3.29 (d, J = 3.0 Hz, 1H), 2.35 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 152.0, 147.8, 143.0, 137.8, 135.6, 129.1, 128.5, 128.4, 128.0, 127.9, 126.4, 123.2, 110.4, 110.1, 108.1, 101.8, 72.7, 72.1, 68.0, 58.8, 57.7, 52.1, 48.4, 27.6, 25.6, 21.4; HRMS (CI) calcd for $C_{31}H_{32}NO_9S$ 594.1798, found 594.1795.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-hydroxy-2,3-(isopropylidenedioxy)-4-[N-benzyl-(4'-methylphenylsulfonyl)amino]-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene (**332a**)

A solution of epoxide **327** (210 mg, 0.36 mmol) in CH_2Cl_2 (25 mL) at –25 °C was treated with a 1.0 M solution of Me_2AlCl in hexanes (400 μL, 0.4 mmol) and stirred at –25 °C

for 2 hours. The reaction was quenched with saturated NH_4Cl solution, and the reaction mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, 4:1 hexanes/ethyl acetate) to furnish tosylamide **332a** (161 mg, 77 %) as a white solid: R_f 0.44 (1:1 hexanes/ethyl acetate); m.p. 114-116 °C; $[\alpha]^{27}_D$ –49.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3504, 1484, 1329, 1238, 1156, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 7.19 (m, 5H), 6.75 (s, 1H), 6.43 (S, 1H), 5.89 (s, 2H), 4.75 (dd, J = 9.7, 7.4 Hz, 1H), 4.58 (d, J = 15.1 Hz, 1H), 4.55-4.43 (m, 3H), 4.28 (t, J = 7.4 Hz, 1H), 4.21 (dd, J = 5.9, 4.5 Hz, 1H), 3.89 (dd, J = 11.2, 7.1 Hz, 1H), 3.69 (dd, J =9.4, 6.6 Hz, 1H), 2.47 (dd, J = 11.6, 4.2 Hz, 1H), 2.42 (s, 3H), 1.92 (s, 1H), 1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 145.9, 143.2, 137.9, 136.1, 129.3, 128.7, 128.2, 128.1, 127.8, 127.6, 123.4, 111.1, 109.8, 104.1, 100.9, 81.0, 75.9, 73.3, 70.9, 67.4, 64.3, 52.4, 39.8, 27.1, 25.0, 21.5; HRMS (CI) calcd for $C_{31}H_{34}NO_8S$ 580.2005, found 580.2001; Anal. Calcd for $C_{31}H_{33}NO_8S$: C, 64.23; H, 5.74; N, 2.42. Found: C, 63.97; H, 5.87; N, 2.36.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)-4-[N-benzyl-(4'-methylphenylsulfonyl)amino]-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene (**332b**)

To a suspension of NaH (35 mg, 60 % reagent, 0.88 mmol) in THF (5 mL) was added a solution of tosylamide **332a** (354 mg, 0.611 mmol) in THF (8 mL). The resulting solution was allowed to stir for 20 minutes after which a solution of di-*tert*-butyl dicarbonate (202 mg, 0.926 mmol) in THF (3 mL) was added dropwise. The resulting solution was heated at reflux for 1.5 hours. After allowing the solution to cool to room temperature, the reaction was quenched with water and then diluted with ethyl acetate.

Following separation of the organic and aqueous phases, the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. The resulting residue was purified by chromatography (silica gel, 1:1 hexanes/ethyl acetate) to provide carbonate **332b** (355 mg, 86 %) as a white solid: R_f 0.44 (2:1 hexanes/ethyl acetate); m.p. 197-198 °C; $[\alpha]^{25}_D$ –43.3 (*c* 1.0, $CHCl_3$); IR (KBr) ν 1740, 1506, 1488, 1277, 1148, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.22-7.13 (m, 5H), 6.61 (s, 1H), 6.42 (s, 1H), 5.89 (m, 1H), 5.81 (m, 1H), 5.00 (dd, J = 11.9, 7.4 Hz, 1H), 4.81 (m, 1H), 4.61 (ABq, J = 14.7 Hz, 2H), 4.47-4.44 (m, 3H), 4.28 (t, J = 4.7 Hz, 1H), 3.65 (m, 1H), 2.59 (dd, J = 12.2, 3.8 Hz, 1H), 2.43 (s, 3H), 1.29 (m, 12H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 146.7, 145.8, 143.3, 137.9, 135.9, 129.3, 128.9, 128.2, 127.8, 127.7, 123.1, 110.4, 109.9, 104.2, 100.7, 82.3, 78.3, 76.0, 75.4, 73.7, 67.4, 64.3, 52.5, 38.9, 27.4, 27.1, 25.1, 21.5; HRMS (FAB) calcd for $C_{36}H_{42}NO_{10}S$ 680.2529, found 680.2528; Anal. Calcd for $C_{36}H_{41}NO_{10}S$: C, 63.61; H, 6.08; N, 2.06. Found: C, 63.78; H, 6.18; N, 2.04.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-benzylamino-1-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene (**332c**)

A solution of tosylamide **332b** (235 mg, 0.346 mmol) in DME (1.5 mL) cooled to –50 °C was treated with a 0.6 M solution of Na/naphthalene in DME until the color of the solution remained dark. The reaction was stirred at –50 °C for 15 minutes and then quenched with saturated NH_4Cl solution. After separation of the organic and aqueous phases, the aqueous phase was extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure.

The remaining residue was purified by chromatography (silica gel, 3:1 hexanes/ethyl acetate) to give carbonate **332c** (140 mg, 77 %) as a white solid: R_f 0.21 (2:1 hexanes/ethyl acetate); m.p. 196-197 °C; $[\alpha]^{26}_D$ –53, 4 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3340, 1736, 1488, 1370, 1239, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m, 5H), 6.60 (s, 1H), 6.39 (s, 1H), 5.83 (m, 1H), 5.74 (m, 1H), 5.07 (dd, J = 11.7, 7.8 Hz, 1H), 4.69 (Abq J = 14.7 Hz, 2H); 4.36 (t, J = 6.6 Hz, 1H), 4.12 (t, J = 6.6 Hz, 1H), 3.86 (m, 2H), 3.79 (t, J = 3.8 Hz, 1H), 3.12 (dd, J = 6.9, 4.2 Hz, 1H), 2.60 (dd, J = 11.4, 3.0 Hz, 1H), 1.69 (s, 1H); 1.36 (s, 3H), 1.27-1.26 (m, 12H); ^{13}C NMR (75 MHz, acetone) δ 153.1, 147.5, 146.6, 129.0, 128.9, 127.4, 125.6, 111.0, 109.9, 104.9, 101.6, 81.8, 78.6, 78.2, 77.8, 77.3, 68.4, 60.5, 52.6, 39.0, 28.1, 27.6, 26.0; HRMS (FAB) calcd for $C_{29}H_{36}NO_8$ 526.2441, found 526.2477.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-hydroxy-2,3-(isopropylidenedioxy)-6-(2'-methoxyethoxy)-4-[N-benzyl-(4'-methylphenylsulfonyl)amino]-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene (**337**)

A degassed solution of tosylamide **332a** (320 mg, 0.55 mmol) and 2-methoxyethanol (0.33 mL, 4.2 mmol) in CH_2Cl_2 (25 mL) was treated with DDQ (188 mg, 0.828 mmol). The resulting solution was stirred at room temperature for 23 hours. The solvent was removed under reduced pressure and the remaining residue was purified by chromatography (silica gel, 2.5:2:1 hexanes/ethyl acetate/triethylamine) to afford acetal **337** (282 mg, 78 %) as a white solid: R_f 0.31 (1:1 hexanes/ethyl acetate); m.p. 87-90 °C; $[\alpha]^{27}_D$ + 2.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3448, 1485, 1328, 1242, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.19-7.13 (m, 5H), 6.72 (s, 1H), 6.69 (s, 1H), 5.91 (m, 2H), 5.46 (s, 1H), 4.73-4.62 (m, 2H), 4.44 (ABq, J = 15.3 Hz, 2H), 4.30 (t, J = 7.3 Hz, 1H), 3.93-3.86 (m, 3H), 3.71-3.59 (m, 3H), 3.43 (s,

3H), 2.42 (s, 3H), 2.38 (d, J = 12.0 Hz, 1H), 2.07 (s, 1H), 1.35-1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 146.9, 143.1, 137.8, 135.7, 129.2, 129.0, 128.2, 128.0, 127.7, 127.3, 124.5, 110.5, 109.8, 107.1, 101.0, 96.8, 81.1, 73.7, 72.0, 69.7, 68.3, 67.2, 63.6, 59.0, 52.5, 39.6, 27.1, 24.9, 21.5; HRMS (FAB) calcd for $C_{34}H_{40}NO_{10}S$ 654.2373, found 654.2409.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-hydroxy-2,3-(isopropylidenedioxy)-4-[N-benzyl-(4'-methylphenylsulfonyl)amino]2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthren-6-one (**338**)

A solution of acetal **337** (158 mg, 0.242 mmol) in 30 % aqueous THF (3.4 mL) was treated with CSA (56 mg, 0.24 mmol) and stirred at room temperature for 17 hours. The solution was then diluted with ethyl acetate and washed successively with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then concentrated *in vacuo*. To a solution of the remaining residue in CH_2Cl_2 (8 mL) along with several 3 Å molecular sieves was added PCC (85 mg, 0.39 mmol). The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was then filtered over Celite which was subsequently washed with several portions of CH_2Cl_2. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, 1:1 hexanes/ethyl acetate) provided lactone **338** (98 mg, 68 %) as a white solid: R_f 0.29 (1:1 hexanes/ethyl acetate); m.p. 145-148 °C; $[\alpha]^{28}_D$ –45.1 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3483, 1719, 1483, 1326, 1259, 1156, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.24-7.14 (m, 5H), 6.72 (s, 1H), 6.05 (m, 2H), 5.24 (t, J = 4.5 Hz, 1H), 4.88 (t, J = 8.0 Hz, 1H), 4.45 (ABq J = 15.3 Hz, 2H), 4.33 (t, J = 7.2 Hz, 1H), 3.92 (m, 1H), 3.78 (dd, J = 8.3, 5.0 Hz, 1H), 2.86 (dd, J = 11.6, 4.1 Hz, 1H), 2.44 (s, 3H), 2.04 (bs, 1H), 1.31 (s, 3H), 1.21 (s,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 152.1, 148.1, 143.9, 137.0, 135.1, 133.3, 129.6, 128.9, 128.5, 128.0, 127.9, 117.7, 109.8, 109.7, 109.2, 102.1, 80.8, 79.7, 74.4, 69.2, 63.4, 52.6, 40.3, 27.1, 25.1, 21.5; HRMS (CI) calcd for $C_{31}H_{32}NO_9S$ 594.1798, found 594.1858.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-benzylamino-1-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)-6-(2'-methoxyethoxy)-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene (**344**)

To a suspension of NaH (12 mg, 0.50 mmol) in THF (5 mL) was added a solution of acetal **337** (208 mg, 0.319 mmol) in THF (8 mL). The resulting solution was stirred at room temperature for 20 minutes after which a solution of di-*tert*-butyl dicarbonate (105 mg, 0.481 mmol) in THF (2 mL) was added dropwise. The solution was heated at reflux for 5 hours. After allowing the solution to cool to room temperature, the reaction was quenched with water and then extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the remaining residue in DME (5 mL) cooled to –50 °C was treated with a 0.6 M solution of Na/naphthalene in DME until a dark color persisted. The resulting solution was stirred at –50 °C for 30 minutes and then quenched with water. After warming the solution to room temperature, the reaction mixture was extracted with ethyl acetate (3 x 25 mL), and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, 3:1:1 hexanes/ethyl acetate/triethylamine) gave carbonate **344** (163 mg, 85 %) as a white foam: R_f 0.24 (1:1 hexanes/ethyl acetate); $[\alpha]^{25}_D$ +21.5 (*c* 1.0, $CHCl_3$) IR (KBr) ν 3448, 1751, 1508, 1490, 1243, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.32 (m, 5H), 6.74 (s, 1H), 6.63 (s, 1H), 5.86 (d, J = 18.0 Hz, 2H), 5.64 (s, 1H), 5.09 (dd, J = 11.7, 7.8 Hz, 1H), 4.43-4.38 (m, 2H), 4.20 (t, J = 5.9 Hz, 1H), 4.01-3.82 (m, 4H), 3.58 (m, 2H), 3.34 (s, 3H),

3.23 (dd, J = 6.7, 3.3 Hz, 1H), 2.64 (dd, J = 11.6, 2.9 Hz, 1H), 1.69 (bs, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.7, 147.3, 140.3, 128.9, 128.7, 127.6, 126.6, 112.6, 110.2, 109.9, 108.1, 101.3, 98.0, 82.6, 78.0, 77.9, 76.4, 72.4, 69.9, 68.0, 59.4, 59.2, 52.7, 38.8, 28.3, 27.9, 26.4; HRMS (FAB) calcd for $C_{32}H_{42}NO_{10}$ 600.2809, found 600.2813.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-benzylamino-1-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene-6-one (**346**)

A solution of acetal **344** (204 mg, 0.340 mmol) in 30 % aqueous THF (13 mL) was treated with CSA (395 mg, 1.70 mmol) and stirred at room temperature for 21 hours. The solution was then diluted with ethyl acetate and washed successively with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then concentrated *in vacuo*. To a solution of the remaining residue in CH_2Cl_2 (9 mL) along with several 3 Å molecular sieves was added PCC (112 mg, 0.520 mmol). The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was then filtered over Celite which was subsequently washed with several portions of CH_3OH. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, 1:1 hexanes/ethyl acetate) provided lactone **346** (131 mg, 72 %) as a white solid: R_f 0.23 (1:1 hexanes/ethyl acetate); m.p. 201-203 °C; $[\alpha]^{27}_D$ –28.1 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3318, 1733, 1702, 1501, 1485, 1260, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.33-7.26 (m, 5H), 6.72 (s, 1H), 6.05 (m, 1H), 5.96 (m, 1H), 5.07 (dd, J = 11.5, 7.5 Hz, 1H), 4.72 (t, J = 3.5 Hz, 1H), 4.40 (dd, J = 7.5, 5.8 Hz, 1H), 4.22 (t, J = 5.4 Hz, 1H), 3.94 (ABq, J = 12.9 Hz, 2H), 3.48 (dd, J = 5.0, 3.4 Hz, 1H), 2.99 (dd, J = 11.5, 3.4 Hz, 1H), 1.63 (bs, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.30 (s, 9H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 163.5, 152.2, 152.1, 148.1, 139.6, 134.6, 128.8, 128.4, 127.6, 118.9, 110.3, 110.2, 108.7, 102.2, 82.9, 79.3, 77.4, 76.9, 75.2, 58.3, 52.7, 38.8, 28.1, 27.6, 26.2; HRMS (FAB) calcd for $C_{29}H_{34}NO_9$ 540.2234, found 540.2238.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-benzylamino-1,2,3-trihydroxy-2,3,4,4a,6,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene-6-one (**349**)

A solution of carbonate **346** (17.5 mg, 0.0295 mmol) in 3:2 MeOH/H_2O (3.5 mL) was treated with a catalytic amount of sodium benzoate and heated at reflux for 17 hours. After allowing the solution to cool to ambient temperature, the reaction mixture was extracted with ethyl acetate (4 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting residue was dissolved in MeOH (1.2 mL) to which excess *p*-toluenesulfonic acid (95 mg, 0.50 mmol) was added. The resulting solution was stirred at room temperature for 38 hours. The reaction mixture was concentrated *in vacuo* and then diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution. Following separation of the aqueous and organic phases, the aqueous phase was extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remainder was purified by chromatography (silica gel, 9:1 $CHCl_3$/MeOH) to give diol **349** (9.9 mg, 84 % over two steps) as a white solid: R_f 0.28 (9:1 $CHCl_3$/MeOH); m.p. 173-176 °C (dec.); $[\alpha]^{26}_D$ –81.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3417, 1703, 1503, 1482, 1260, 1034 cm^{-1}; ^1H NMR (500 MHz, acetone) δ 7.38 (d, J = 7.4 Hz, 2H), 7.32 (s, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.89 (s, 1H), 6.10 (m, 2H), 4.75 (td, J = 2.9, 1.3 Hz, 1H), 4.14 (m, 1H), 3.91 (ABq, J = 14.0 Hz, 2H), 3.85 (m, 2H), 3.68-3.38 (m, 4H); 3.32 (t, J = 2.6 Hz, 1H), 3.11 (m, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 164.8, 152.0, 147.5, 137.8, 129.8, 128.5, 128.3, 128.1, 117.2, 109.7, 108.9, 101.9, 78.7, 72.8, 69.8, 59.4, 52.3, 41.1; HRMS (FAB) calcd for $C_{21}H_{22}NO_7$ 400.1396, found 400.1312.

(1*S*,2*R*,3*S*,4*R*,4a*S*,11b*R*)-2-benzylamino-1,3,4-trihydroxy-1,2,3,4,4a,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene-6-one (**350**)

A solution of triol **349** (43 mg, 0.11 mmol) in MeOH (4 mL) was treated with K_2CO_3 (31 mg, 0.22 mmol) and then heated at reflux for 13 hours. The reaction was quenched with saturated NH_4Cl solution and then diluted with ethyl acetate. The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (4 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, 9:1 $CHCl_3$/MeOH) to give triol **350** (19 mg, 44 %) as a thin film: R_f 0.42 (9:1 $CHCl_3$MeOH); $[\alpha]^{25}_D$ –60.4 (*c* 1.0, $CHCl_3$); IR (neat) ν 3410, 1690, 1484, 1261, 1026 cm^{-1}; ^1H NMR (500 MHz, acetone) δ 7.40 (d, J = 7.2 Hz, 2H), 7.36 (s, 1H), 7.30 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 0.8 Hz, 1H), 6.10 (m, 2H), 4.68 (s, 1H), 4.58 (dd, J = 12.2, 9.4 Hz, 1H), 4.37 (s, 1H), 4.27 (td, J = 3.2, 1.3 Hz, 1H), 4.22 (dd, J = 9.4, 3.2 Hz, 1H), 3.91 (s, 2H), 3.45 (ddd, J = 12.3, 2.6, 0.7 Hz, 1H), 3.38 (t, J = 2.8 Hz, 1H), 3.0-2.62 (m, 3H); ^{13}C NMR (126 MHz, acetone) δ 163.8, 152.5, 147.0, 140.8, 138.0, 128.3, 126.9, 120.1, 108.7, 105.6, 102.3, 78.5, 74.2, 70.3, 69.1, 60.3, 52.0, 39.7; HRMS (FAB) calcd for $C_{21}H_{22}NO_7$ 400.1396, found 400.1379.

(1S, 2R, 3S, 4R, 4aS, 11bR)-2-benzylamino-1,3,4-triacetoxy-1,2,3,4,4a,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene-6-one (**352**)

A solution of triol **350** (8.2 mg, 0.016 mmol) in pyridine (0.25 ml) was treated with neat acetic anhydride (58 µL, 0.61 mmol) followed by a catalytic amount of DMAP. The reaction was stirred for 32 hours. The solvent was removed and the remainder purified by chromatography (silica gel, 1:1 hexanes/ethyl acetate) to give triacetate **352** (6.6 mg, 61 %) as an oil: R_f 0.44 (1:1 hexanes/ethyl acetate); $[\alpha]^{26}_D$ −16.2 (*c* 1.0, $CHCl_3$); IR (neat) ν 3441, 1742, 1505, 1485, 1372, 1230, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.38-7.28 (m, 5H), 6.40 (s, 1H), 6.06 (m, 2H), 5.61-5.56 (m, 2H), 5.52 (m, 1H), 4.91 (dd, J = 12.2, 20.7 Hz, 1H), 3.96 (ABq, J = 13.2 Hz, 2H); 3.77 (dd, J = 12.3, 3.0 Hz, 1H), 3.30 (t, J = 2.6 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.7 Hz (bs, 1H); HRMS (FAB) calcd for $C_{27}H_{28}NO_{10}$ 526.1713, found 526.1718.

(1S, 2R, 3S, 4R, 4aS, 11bR)-2-acetylamino-1,3,4-triacetoxy-1,2,3,4,4a,11b-hexahydro-1H-5,8,10-trioxa-cyclopenta[b]phenanthrene-6-one (**353**)

A solution of triacetate **352** (5.7 mg, 0.011 mmol) and $Pd(OH)_2$ (25 mg) in MeOH (1.5 ml) was subjected to an atmosphere of hydrogen for 40 minutes. The reaction was filtered over Celite and the filtrate concentrated *in vacuo*. The remaining residue was dissolved in pyridine (0.15 mL) to which acetic anhydride (15 µL, 0.16 mmol) was added followed by a cataytic amount of DMAP. The reaction was allowed to stir for 19 hours. The solvent was removed and the residue purified by chromatography (silica gel, 1:1 hexanes/ethyl acetate) to provide tetraacetate **353** (2.8 mg, 55 %) as a film: ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.62 (s, 1H), 6.06 (m, 2H), 5.71 (s, 1H), 5.53-5.46 (m, 2H), 4.89 (dd, J = 12.2, 10.1 Hz, 1H), 4.54 (m, 1H), 3.53 (dd, J = 10.5, 1.8 Hz, 1H); 2.08 (m, 9H), 1.98 (s, 3H).

N-[(1*R*,2*S*,5*R*,6*S*)-2-(Benzo[1,3]dioxol-5-ylmethoxy)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4'-methylbenzenesulfonamide (**354**)

To a suspension of KH (108 mg, 2.69 mmol) in DME (3 mL) was added a solution of piperonol (378 mg, 2.49 mmol) in DME (5 mL). The resulting solution was allowed to stir for 20 minutes after which a solution of vinylaziridine **28** (228 mg, 0.710 mmol) in DME (3 mL) was added dropwise followed by 18-crown 6 (66 mg, 0.25 mmol). The reaction was stirred for 24 hours and then quenched with saturated NH_4Cl solution. The reaction mixture was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic extracts dried over Na_2SO_4. The solvent was removed under reduced pressure and the remainder purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to furnish tosylamide **354** (223 mg, 56 %) as a white foam: R_f 0.38 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{29}$ –10.5 (*c* 1.0, $CHCl_3$); IR (neat) ν 3269, 1503, 1599, 1492, 1445, 1326, 1251, 1156, 1094, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 6.68 (dd, J = 7.9, 1.8 Hz, 1H), 5.94 (s, 2H), 5.88 (dd, J = 10.3, 1.0 Hz, 1H), 5.84 (ddd, J = 10.1, 3.2, 1.8 Hz, 1H), 5.10 (d, J = 7.4 Hz, 1H), 4.53 (dd, J = 6.3 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 4.05 (dd, J = 9.4, 6.1 Hz, 1H), 3.80 (dq, J = 9.2, 1.6 Hz, 1H), 3.55 (td, J = 9.2, 7.4 Hz, 1H), 2.37 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 147.2, 142.9, 139.0, 132.6, 131.9, 129.3, 127.6, 124.5, 121.6, 110.8, 109.0, 108.2, 101.0, 76.4, 75.7, 72.2, 70.8, 57.3, 27.8, 26.0, 21.7; HRMS (FAB) calcd for $C_{24}H_{28}NO_7S$ 474.1586, found 474.1587.

N-Benzyl-N-[(1*R*,2*S*,5*R*,6*S*)-2-(Benzo[1,3]dioxol-5-ylmethoxy)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4'-methylbenzenesulfonamide (**355**)

To a suspension of NaH (10.8 mg of 60 % reagent, 0.270 mmol) in THF (2 mL) was added a solution of tosylamide **354** (117 mg, 0.208 mmol) in THF (5 mL). The resulting solution was stirred for 20 minutes after which benzyl bromide (36 μL, 0.28 mmol) was added followed by a catalytic amount of tetrabutylammonium iodide. The solution was stirred for 18 hours and then quenched with water. The reaction was diluted with ethyl acetate and the aqueous and organic layers separated. The aqueous phase was extracted with ethyl acetate (4 x 40 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent *in vacuo* provided a residue which was purified by chromatography (silica gel, 3:1 hexanes/ethyl acetate) generating tosylamide **355** (114 mg, 84 %) as a solid: R_f 0.21 (5:1 hexanes/ethyl acetate); m.p. 157-160 °C; $[\alpha]_D^{25}$ +3.2 (*c* 1.0, $CHCl_3$); IR (neat) ν 1599, 1503, 1492, 1445, 1330, 1251, 1156, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 2H), 7.22-7.15 (m, 7H), 6.81-6.78 (m, 3H), 5.97-5.94 (m, 3H), 5.80 (d, J = 9.9 Hz, 1H), 4.57-4.31 (m, 6H), 2.40 (s, 3H), 1.32-1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 142.9, 138.1, 136.4, 133.0, 131.7, 129.1, 128.9, 128.2, 127.5, 123.0, 121.6, 112.0, 110.3, 108.9, 107.9, 100.9, 73.6, 72.7, 70.6, 27.5, 25.7, 21.5; HRMS (FAB) calcd for $C_{31}H_{34}NO_7S$ 564.2056, found 564.2099.

N-Benzyl-N-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-3,4-dihydroxy-5,6-(isopropylidenedioxy)-2-(3',4'-methylenedioxyphenylmethyl)cyclohex-1-yl]-4'-methylbenzenesulfonamide (**356**)

A solution of tosylamide **355** (16.2 mg, 0.0288 mmol) in 1:1 CH_3CN/EtOAc (0.80 mL) at 0 °C was treated with a solution of $NaIO_4$ (10.1 mg, 0.0432 mmol) and $RuCl_3 H_2O$ in water (0.5 mL). The resulting solution was stirred at 0 °C for 3 minutes and then quenched with saturated $Na_2S_2O_3$ solution. The reaction mixture was extracted with

CH_2Cl_2 (4 x 10 mL) and the combined organic extracts dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, 2:1 ethyl acetate/hexanes) to provide diol **356** (11.3 mg, 66 %) as a film: R_f 0.34 (2:1 ethyl acetate/hexanes); $[\alpha]_D^{26}$ –27.9 (*c* 1.0, $CHCl_3$); IR (neat) ν 3460, 1504, 1492, 1445, 1328, 1251, 1156, 1040 cm^{-1}; ^1H NMR (300 MHz, acetone) δ 7.75 (d, J = 7.8 Hz, 2H), 7.24-7.15 (m, 7H), 6.88 (s, 1H); 6.80-6.78 (m, 2H), 6.00 (s, 2H), 4.60 (d, J = 11.1 Hz, 1H), 4.45-4.38 (m, 3H), 4.28-4.14 (m, 4H), 4.03-3.79 (m, 3H), 3.93 (bs, 1H), 2.38 (s, 3H), 1.28-1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.3, 142.8, 138.3, 136.2, 131.8, 129.1, 128.8, 128.2, 128.0, 127.5, 122.1, 109.3, 109.2, 108.1, 101.0, 76.5, 73.0, 69.7, 27.4, 25.4, 21.4; HRMS (FAB) calcd for $C_{31}H_{36}NO_9S$ 598.2111, found 598.2108.

N-Benzyl-N-[(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-dihydroxy-5,6-(isopropylidenedioxy)-2-(3',4'-methylenedioxyphenylmethyl)cyclohex-1-yl]-4'-methylbenzenesulfonamide (**357**)

A solution of epoxide **327** (17.2 mg, 0.0297 mmol) in a 1:1 mixture of 1,4-dioxane/H_2O (1 mL) was treated with KOH (16.7 mg, 0.297 mmol) and then heated at reflux for 48 hours. The reaction mixture was diluted with ethyl acetate and the organic and aqueous layers separated. The aqueous layer was extracted with ethyl acetate (4 x 20 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a residue which was purified by chromatography (silica gel, 4:1 ethyl acetate/hexanes) to give diol **357** (9.9 mg, 56 %) as a film: R_f 0.36 (4:1 ethyl acetate/hexanes);$[\alpha]_D^{27}$ –35.4 (*c* 1.0, $CHCl_3$); IR (neat) ν 3478, 1493, 1445, 1326, 1246, 1156, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 2H), 7.24-7.20 (m, 7H), 6.76-6.75 (m, 3H), 5.97 (s, 2H), 4.48 (m, 2H), 4.38-4.24 (m, 3H), 4.10-4.06 (m, 2H), 3.98-3.90 (m, 2H), 3.73 (t, J = 6.0 Hz, 1H), 2.42 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 147.7, 147.4, 143.1, 137.8, 136.3, 131.2, 129.2, 128.8, 128.4, 128.0, 127.7, 122.0, 109.5, 109.1, 108.1, 101.0, 77.8, 75.3, 74.1, 72.5, 70.5, 69.4, 61.0, 50.9, 27.4, 25.2, 21.5; HRMS (FAB) calcd for $C_{31}H_{35}NO_9S$ + Na 620.1930, found 620.1910.

(*2R,3R,4S,5R*)-2-(Benzo[1,3]-dioxol-5-ylmethoxy)-3-(N-benzyl-(4'-methylphenylsulfonyl)amino)-1,6-dihydroxy-4,5-(isopropylidenedioxy)hexane (**358**)

A solution of diol **356** (21.1 mg, 0.0353 mmol) in 40 % aqueous acetone (2 mL) was treated with a solution of $NaIO_4$ (10.2 mg, 0.0477 mmol) in water (0.2 mL) and stirred at room temperature for three hours. The reaction mixture was concentrated *in vacuo* and the resulting solution was extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was dissolved in MeOH (1 mL) and cooled to 0 °C after which neat $NaBH_4$ was added. The solution was slowly warmed to room temperature and was stirred for 18 hours. The reaction mixture was treated with water and then concentrated *in vacuo*. The remaining solution was extracted with ethyl acetate (4 x 20 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a residue which was purified by chromatography (silica gel, 2:1 ethyl acetate/hexanes) furnishing diol **358** (11.1 mg, 52 %) as a film: R_f 0.30 (2:1 ethyl acetate/hexanes); $[\alpha]_D^{25}$ + 66.8 (*c* 1.0, $CHCl_3$); IR (neat) ν 3501, 1503, 1491, 1445, 1332, 1251, 1157, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H); 7.36-7.34 (m, 2H), 7.21-1.15 (m, 5H), 6.73 (d, J = 8.7 Hz, 1H), 6.62-6.60 (m, 2H), 5.93 (m, 2H), 4.60 (d, J = 15.9 Hz, 1H), 4.39-4.27 (m, 4H), 4.13 (d, J = 11.7 Hz, 1H), 3.93 (m, 1H), 3.69-3.58 (m, 2H), 3.44-3.40 (m, 4H), 2.37 (s, 3H), 2.03 (bs, 1H), 1.13 (s, 3H), 1.0 (s,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.5, 143.0, 138.1, 137.0, 131.2, 128.8, 128.0, 127.7, 126.8, 121.9, 108.8, 108.0, 107.9, 101.1, 78.5, 73.2, 72.3, 61.2, 58.9, 55.2, 49.6, 27.7, 25.0, 21.4; HRMS (FAB) calcd for $C_{31}H_{38}NO_9S$ 600.2267, found 600.2264. (Note: An analagous procedure can be applied to diol **357** which also affords diol **358**).

(1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-2,3-dihydroxy-4,5-(isopropylidenedioxy)-7-(4'-methylphenylsulfonyl)-7-azabicyclo[4.1.0]heptane (**359**)

A solution of vinylaziridine **28** (595 mg, 1.85 mmol) in a 1:1 mixture of CH_3CN/EtOAc (50 mL) at 0 °C was treated with a solution of $NaIO_4$ (595 mg, 2.78 mmol) and $RuCl_3\,3H_2O$ (32 mg, 0.15 mmol) in H_2O (4 mL). The solution was stirred at 0 °C for 3 minutes and then quenched with 20 % aqueous $Na_2S_2O_3$ solution (20 mL). The organic and aqueous layers were separated and the aqueous phase extracted with ethyl acetate (4 x 40 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, 1:1 hexanes/ethyl acetate) to afford diol **359** (296 mg, 45 %) as a white solid: R_f 0.28 (1:1 hexanes/ethyl acetate); m.p.: 166-168 °C; $[\alpha]_D^{26}$ +6.6 (*c* 1.0, $CHCl_3$); IR (neat) ν 3367, 1329, 1173, 1056 cm^{-1}; ^{1}H NMR (300 MHz, acetone) δ 7.87 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 4.41-4.34 (m, 2H), 4.16 (m, 1H), 3.92 (m, 1H), 3.31 (d, J = 6.6 Hz, 1H), 3.24 (d, J = 9.9 Hz, 1H), 3.05 (d, J = 6.9 Hz, 1H), 2.46 (m, 3H), 1.39 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 133.5, 130.1, 128.0, 110.0, 76.9, 69.2, 68.2, 61.8, 45.2, 43.1, 27.2, 24.8, 21.7; HRMS (FAB) calcd for $C_{16}H_{22}NO_6S$ 356.1168, found 356.1166; Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96. Found: C, 54.04; H, 5.97.

(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-2-(benzoyloxy)-3-hydroxy-4,5-(isopropylidenedioxy)-7-(4'-methylphenysulfonyl)-7-azabicycol[4.1.0]heptane (**361**)

A solution of diol **359** (323 mg, 0.909 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with Et_3N (1.1 mL, 7.9 mmol) followed by sulfuryl chloride (2.73 mL, 1.0 M solution in CH_2Cl_2, 2.73 mmol) and slowly warmed to room temperature. The reaction was stirred for 5 hours and subsequently quenched with water. After separation of the organic and aqueous phases, the aqueous phase was extracted with CH_2Cl_2 (4 x 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by chromatography (5:1 hexanes/ethyl acetate) to provide cyclic sulfate **360** as a solid: R_f 0.44 (3:1 hexanes/ethyl acetate); m.p.: 208-211 °C; $[\alpha]_D^{24}$ –51.8 (*c* 1.0, $CHCl_3$); IR (neat) ν 1394, 1330, 1212, 1164, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 5.26 (m, 1H), 5.01 (d, J = 6.1 Hz, 1H), 4.62 (d, J = 5.6 Hz, 1H), 4.54 (d, J = 4.1 Hz, 1H), 3.54 (d, J = 6.4 Hz, 1H), 3.38 (dd, J = 6.1, 3.8 Hz, 1H), 2.46 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, acetone) δ 146.2, 135.1, 130.7, 129.3, 111.3, 78.7, 78.0, 73.7, 69.9, 42.9, 38.6, 27.4, 25.3, 21.7; HRMS (CI) calcd for $C_{16}H_{20}NO_8S_2$ 418.0630, found 418.0639; Anal. Calcd for $C_{16}H_{19}NO_8S_2$: C, 46.04; H, 4.59. Found: C, 46.18; H, 4.49.

A solution of crude sulfate **360** and ammonium benzoate (297 mg, 2.14 mmol) in DMF (7 mL) was heated at 70 °C for two hours. The solvent was removed under vacuum and the residue dissolved in THF (20 mL) to which H_2O (30 μL) and concentrated H_2SO_4 (30 μL) were added. The resulting solution was stirred at room temperature for one hour and then quenched with saturated $NaHCO_3$ solution (5 mL). The reaction mixture was diluted with ethyl acetate, and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (4 x 50 mL) and the combined organic

extracts dried over Na_2SO_4. The remainder was purified by chromatography (silica gel, 3:1 hexanes/ethyl acetate) to provide alcohol **361** (213 mg, 51 %) as an oil: R_f 0.26 (3:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +41.6 (*c* 1.0, $CHCl_3$); IR (neat) ν 3494, 1723, 1332, 1270, 1163, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d J = 8.0 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 5.12 (d, J = 5.4 Hz, 1H), 4.56 (d, J = 6.1 Hz, 1H), 4.19 (t, J = 5.7 Hz, 1H), 3.96 (dt, J = 8.1, 5.4 Hz, 1H), 3.33 (m, 2H), 2.73 (d, J = 8.4 Hz, 1H), 2.48 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 145.7, 134.0, 133.7, 130.4, 130.1, 129.4, 128.7, 128.3, 110.2, 75.2, 70.5, 68.4, 68.1, 41.5, 39.7, 27.7, 25.3, 21.9; HRMS (FAB) calcd for $C_{23}H_{26}NO_7S$ 460.1430, found 460.1441.

(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-2-(benzoyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-7-(4'-methylphenysulfonyl)-7-azabicycol[4.1.0]heptane (**362**)

A solution of alcohol **361** (156 mg, 0.341 mmol) in CH_2Cl_2 (8 mL) was treated with imidazole (231 mg, 3.40 mmol) followed by *tert*-butyldimethylsilyl chloride (512 mg, 3.40 mmol). The reaction was stirred at room temperature for 17 hours. The reaction mixture was filtered over Celite and the filtrate concentrated *in vacuo*. The remaining residue was purified by chromatography (silica gel, 6:1 hexanes/ethyl acetate) to give benzoate **362** (158 mg, 81 %) as an oil: R_f 0.47 (5:1 hexanes/ethyl acetate); $[\alpha]_D^{26}$ +20.9 (*c* 1.0, $CHCl_3$); IR (neat) ν 1725, 1599, 1335, 1268, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 4.92 (m, 1H), 4.52 (m, 1H), 3.94-3.90 (m, 2H), 3.34 (d, J = 6.3 Hz, 1H), 3.10 (d, J = 6.0 Hz, 1H), 2.47 (s, 3H), 1.55 (s, 3H), 1.37 (s, 3H), 0.74 (s, 9H), 0.08 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 165.2, 144.8,

134.4, 133.3, 129.9 129.7, 129.3, 128.3, 128.0, 109.6, 76.5, 71.4, 70.9, 70.2, 42.8, 38.8, 28.0, 25.7, 25.5, 21.6, 17.8, -4.7, -4.9; HRMS (FAB) calcd for $C_{29}H_{40}NO_7SSi$ 574.2295, found 574.2293.

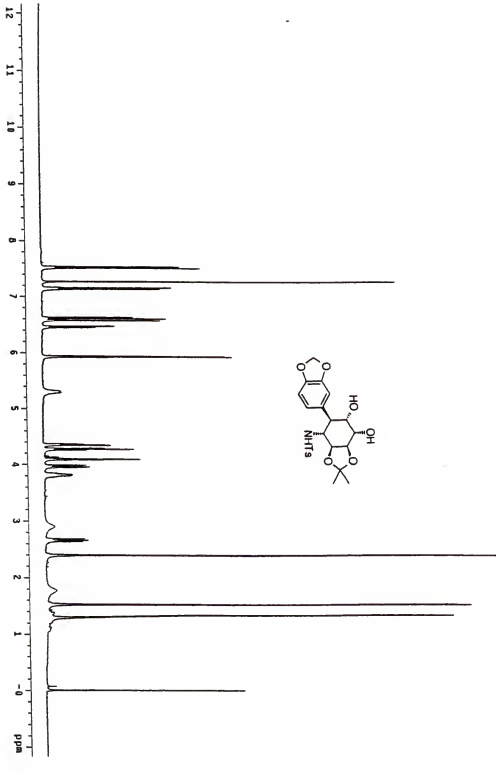
(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-4,5-(isopropylidenedioxy)-7-(4'-methylphenysulfonyl)-7-azabicycol[4.1.0]heptane (**363**)

A solution of benzoate **362** (136 mg, 0.238 mmol) in THF (7 mL) was treated with a 0.5 M sodium methoxide solution (0.57 mL) in methanol. The reaction was stirred for 15 minutes and then quenched with saturated NH_4Cl solution. The organic and aqueous layers were separated and the aqueous phase extracted with ethyl acetate (4 x 35 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, 5:1 hexanes/ethyl acetate) to afford alcohol **363** (54 mg, 48 %) as an oil: R_f 0.23 (5:1 hexanes/ethyl acetate); $[\alpha]_D^{26}$ –5.8 (*c* 1.0, $CHCl_3$); IR (neat) ν 3515, 1332, 1251, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.80 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 4.34 (d, J = 5.4 Hz, 1H), 3.97 (t, J = 5.3 Hz, 1H), 3.88 (t, J = 4.8 Hz, 1H), 3.69 (ddd, J = 9.1, 4.1, 1.4 Hz, 1H), 3.19 (d, J = 6.6 Hz, 1H), 3.04 (d, J = 6.6 Hz, 1H), 2.76 (d, J = 9.0 Hz, 1H), 2.44 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 144.9, 134.9, 129.9, 128.2, 109.7, 76.1, 71.2, 70.3, 68.0, 42.2, 39.2, 28.1, 25.9, 25.8, 21.9, 18.1, -4.7, -4.8; HRMS (FAB) calcd for $C_{22}H_{36}NO_6SSi$ 470.2032, found 470.2020.

APPENDIX

SELECTED SPECTRA

The ^{1}H and ^{13}C or APT NMR spectra of selected compounds reported in Chapter 5 are shown in this appendix along with the proposed structures.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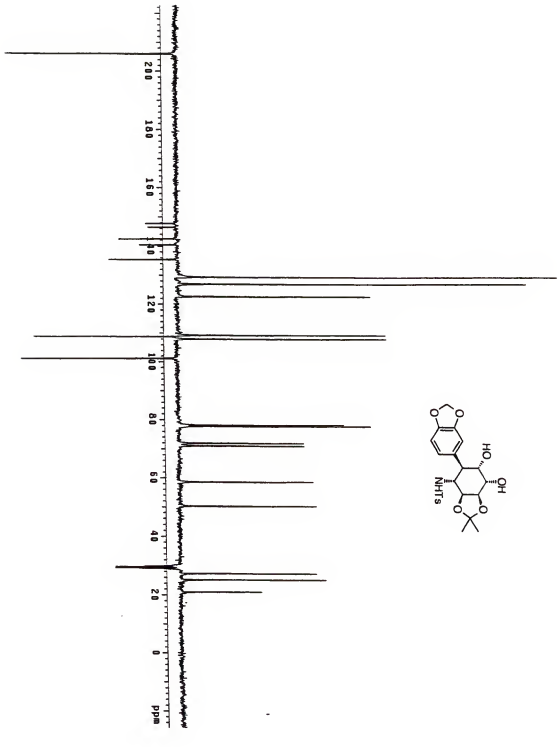
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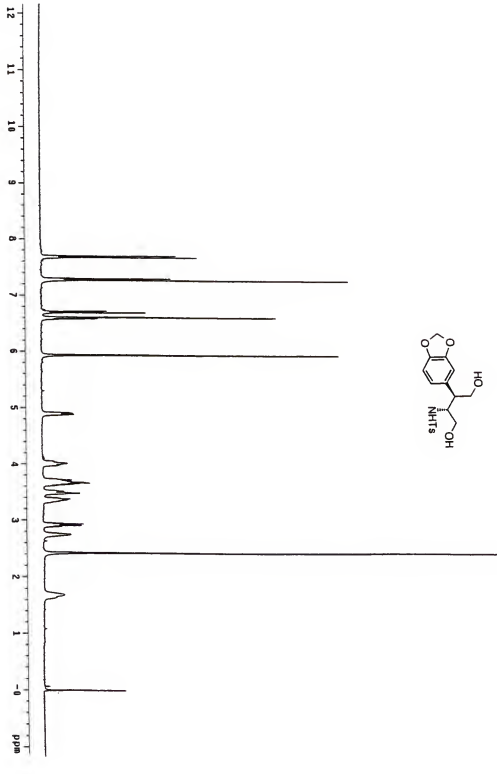
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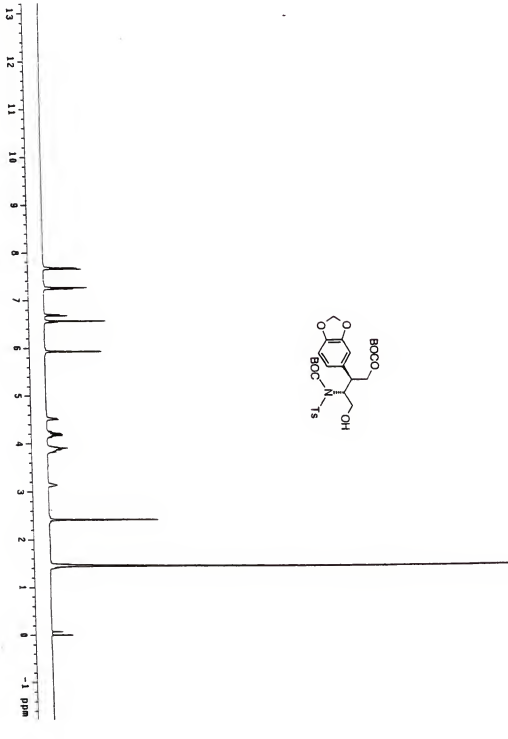
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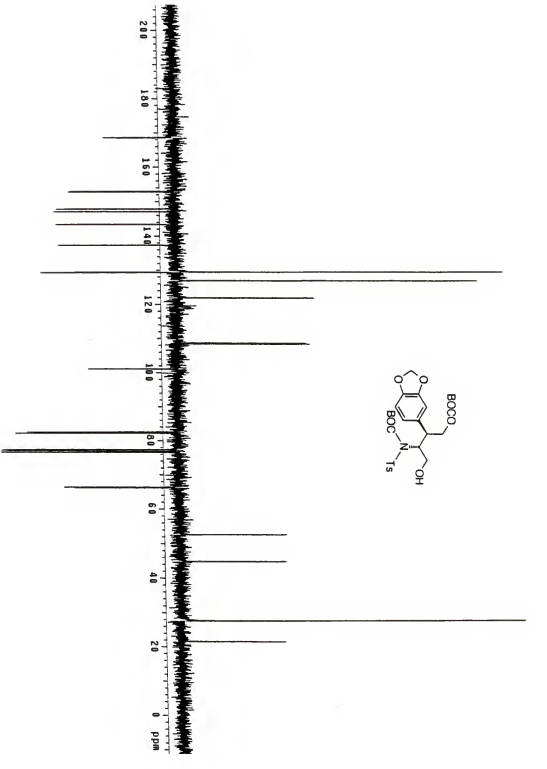
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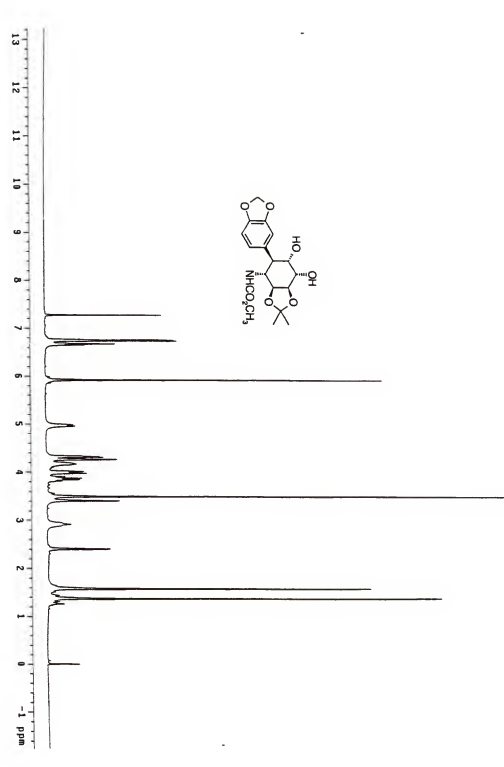
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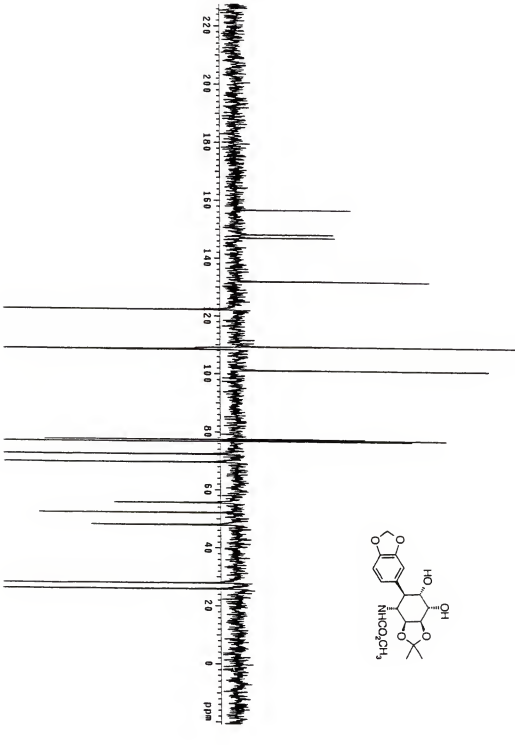
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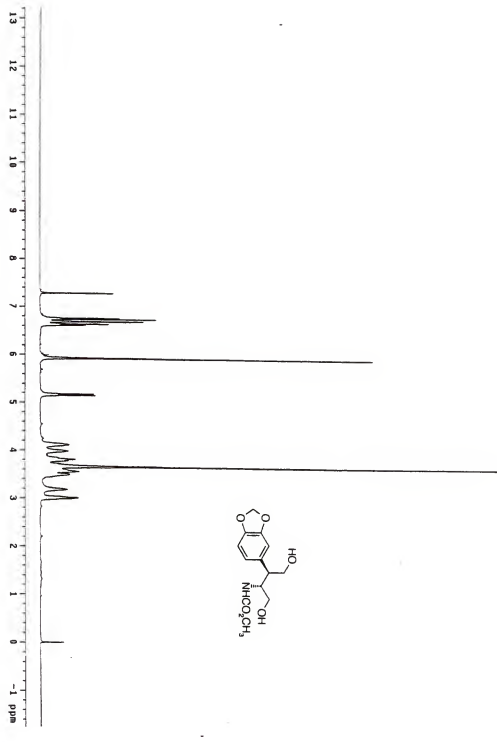
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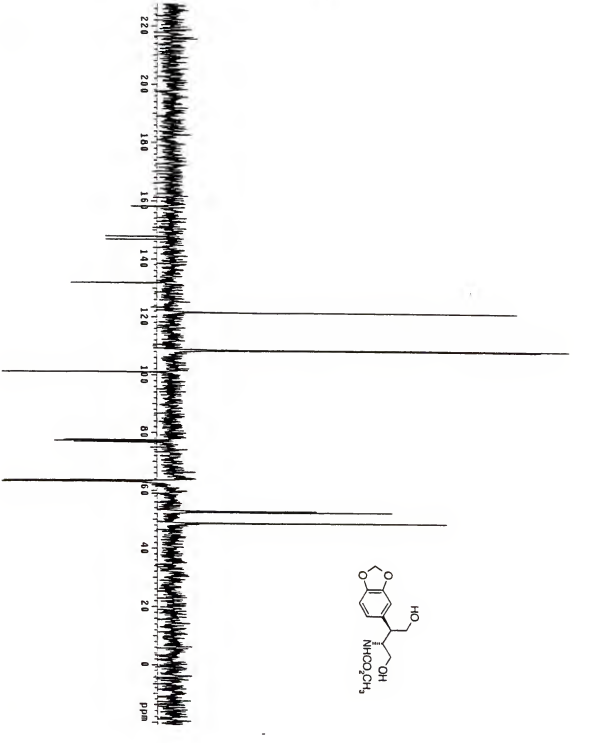
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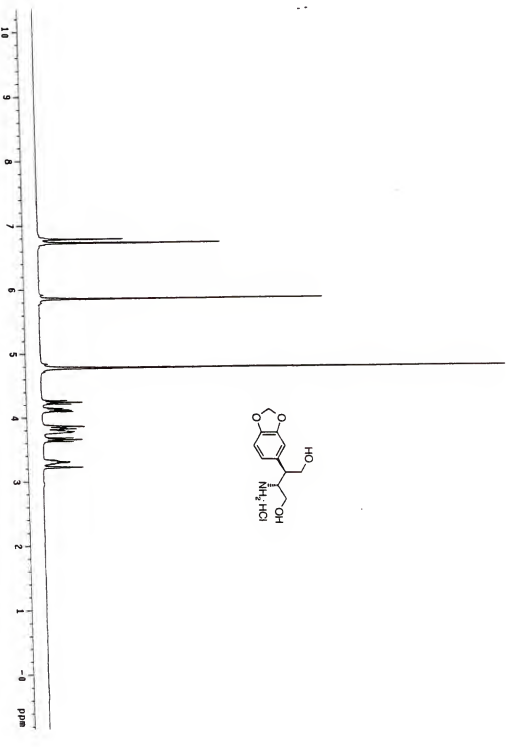
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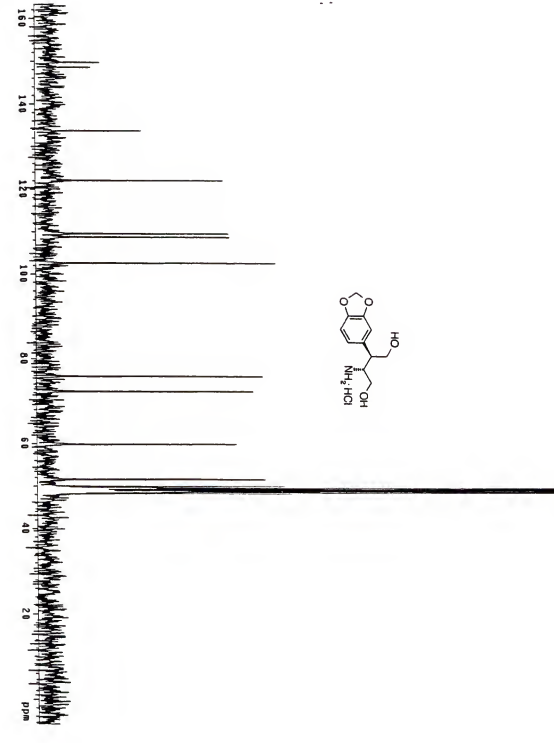
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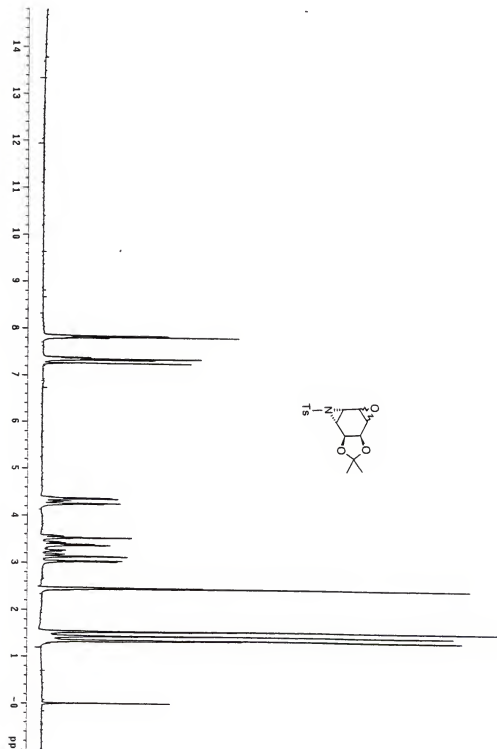
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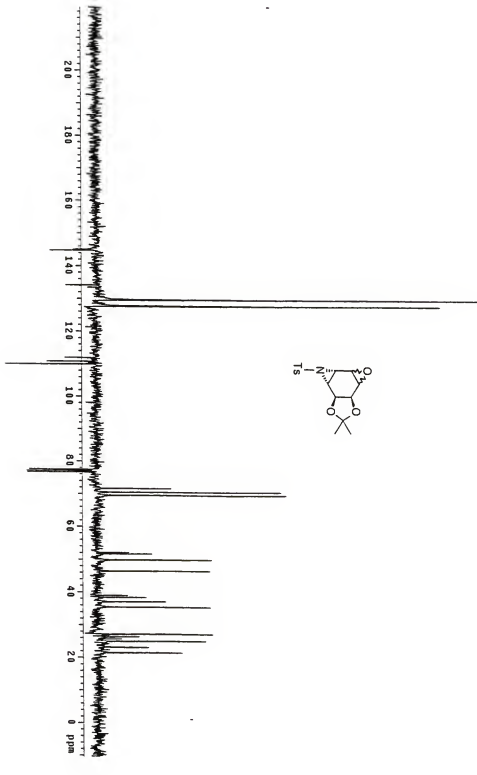
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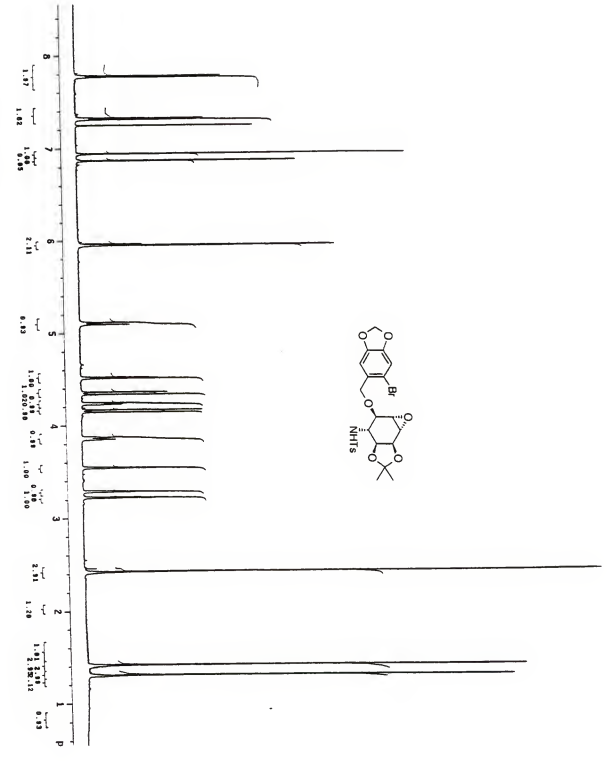
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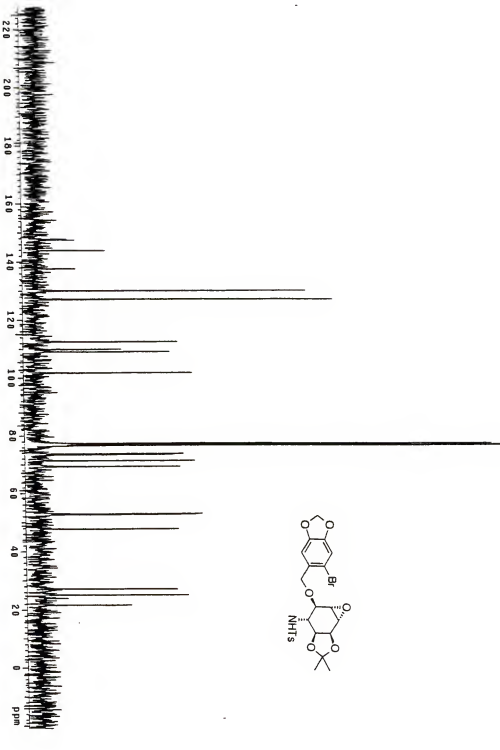
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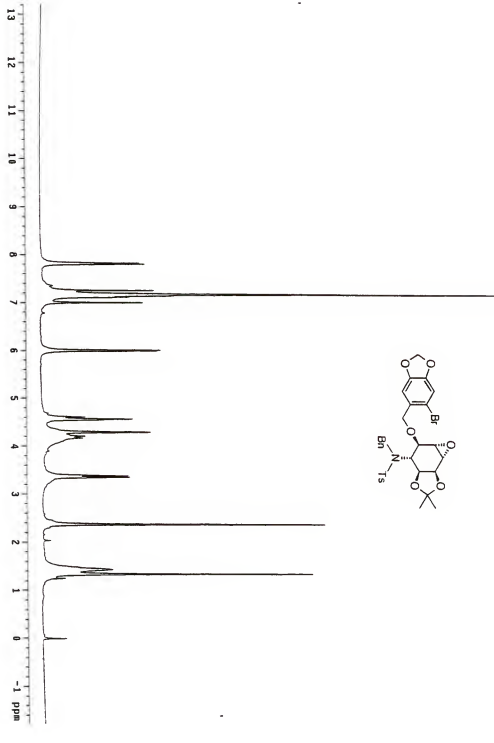
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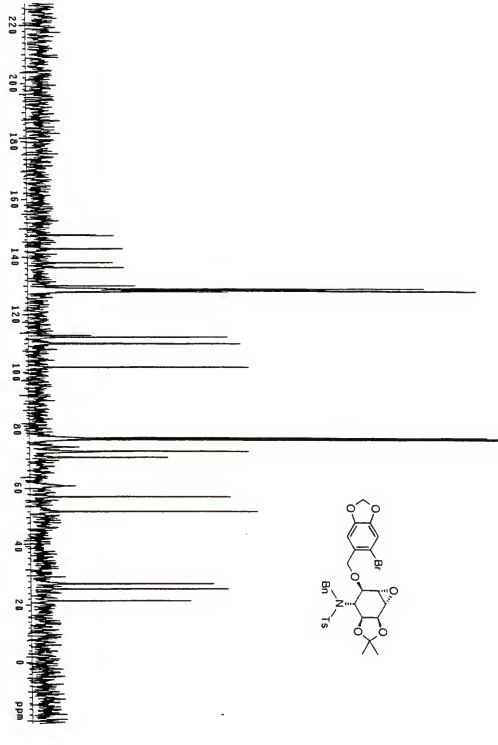
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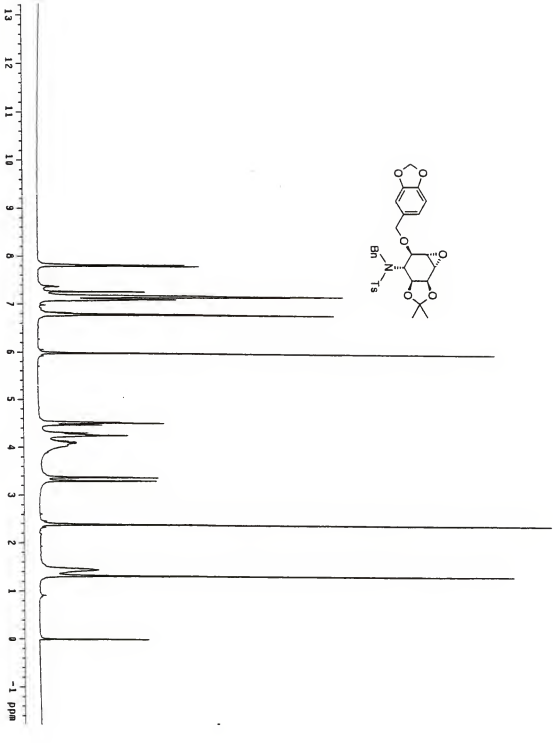
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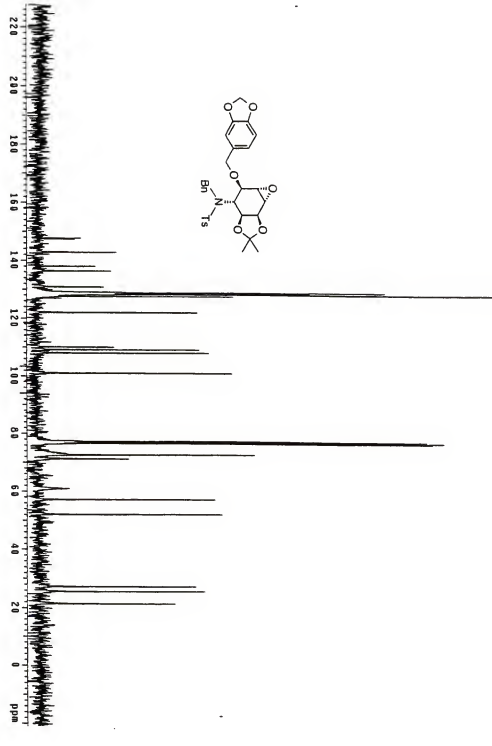
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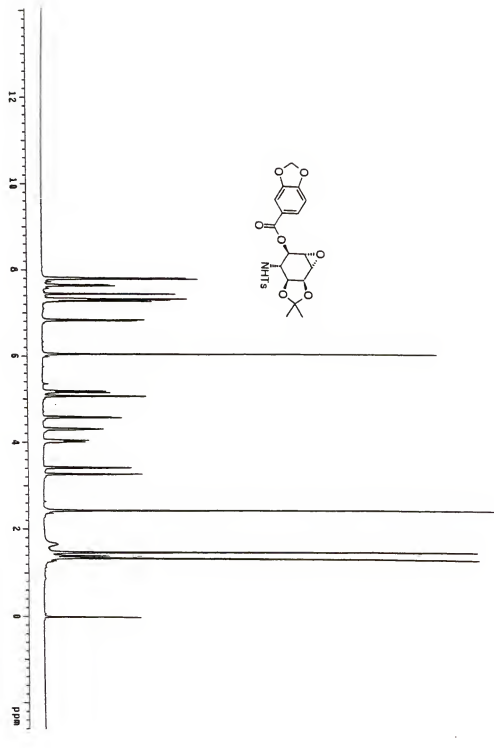
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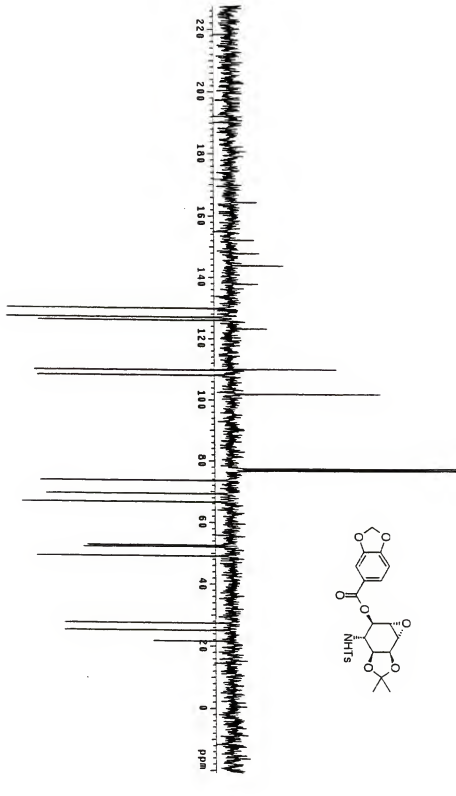
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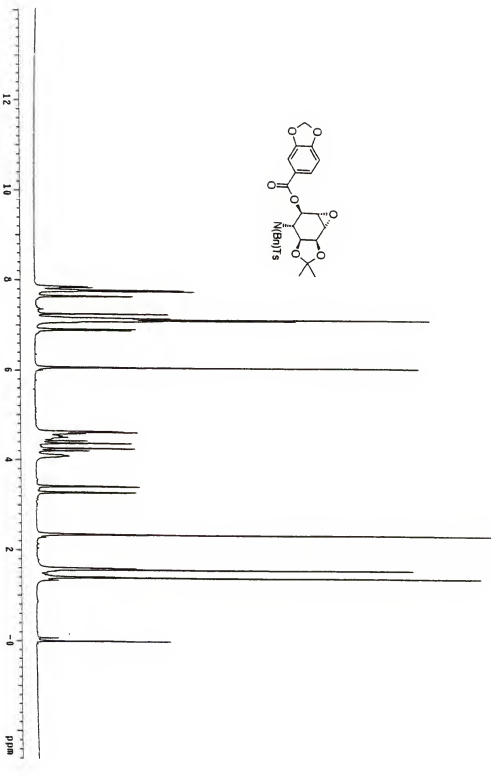
NHTs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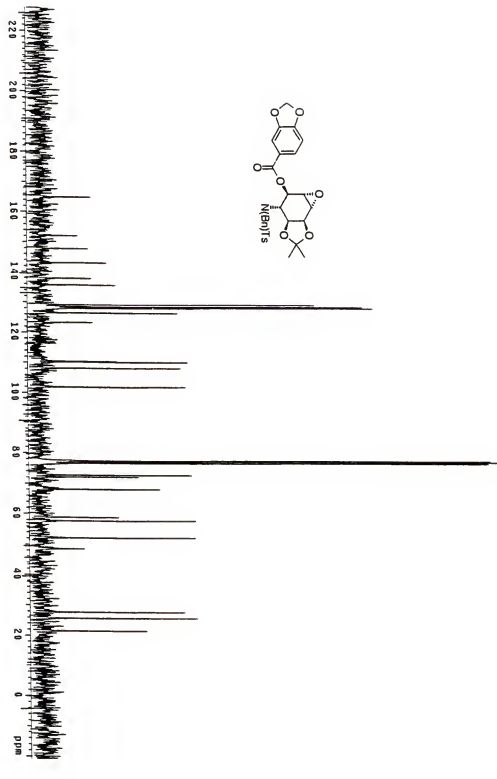
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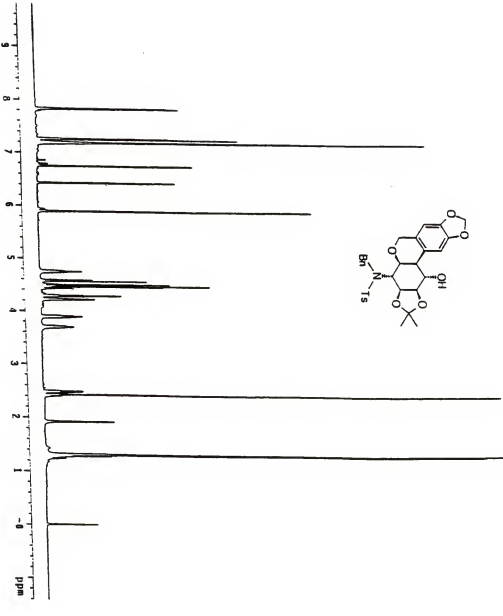
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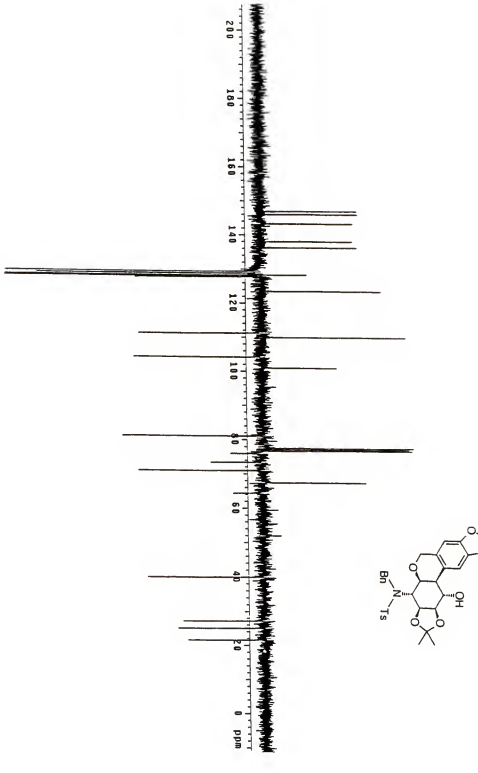
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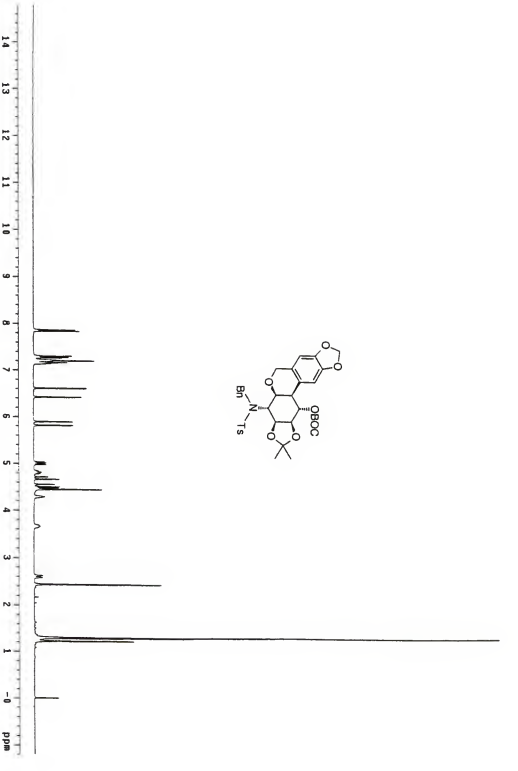
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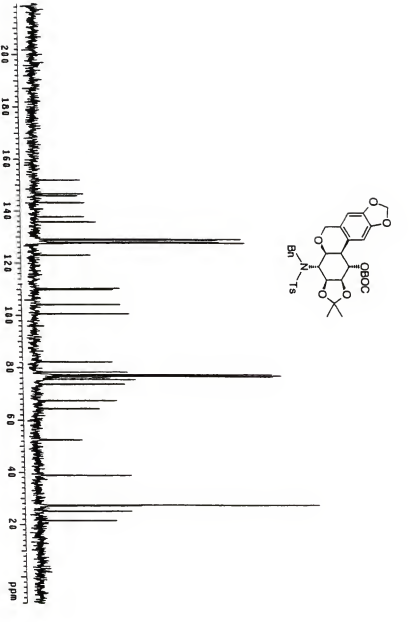
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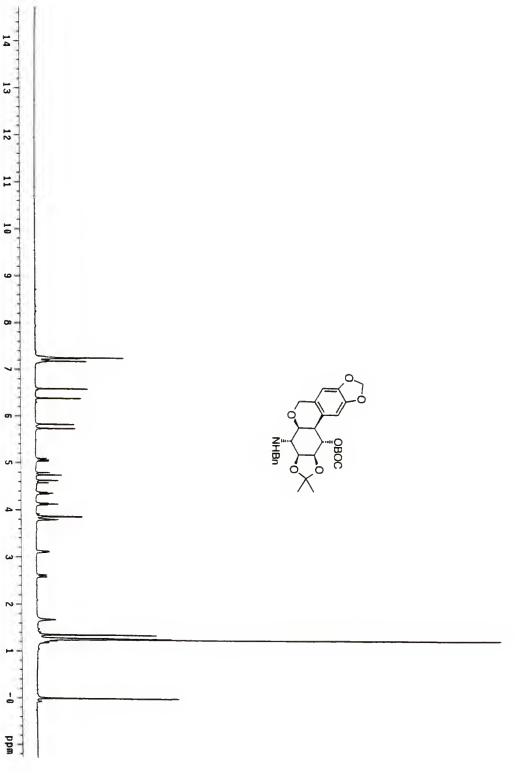
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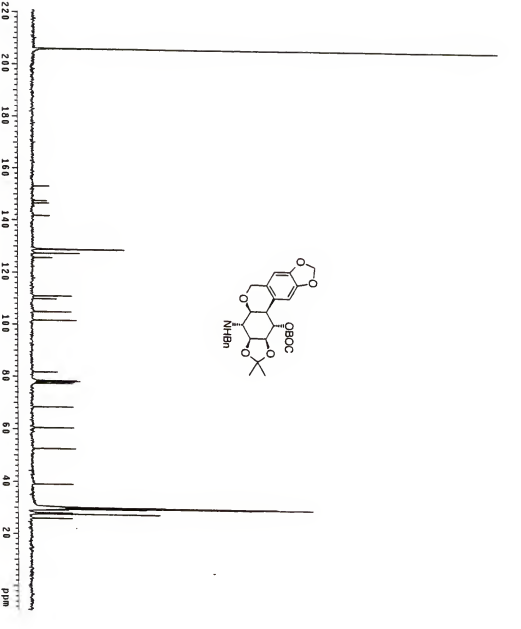
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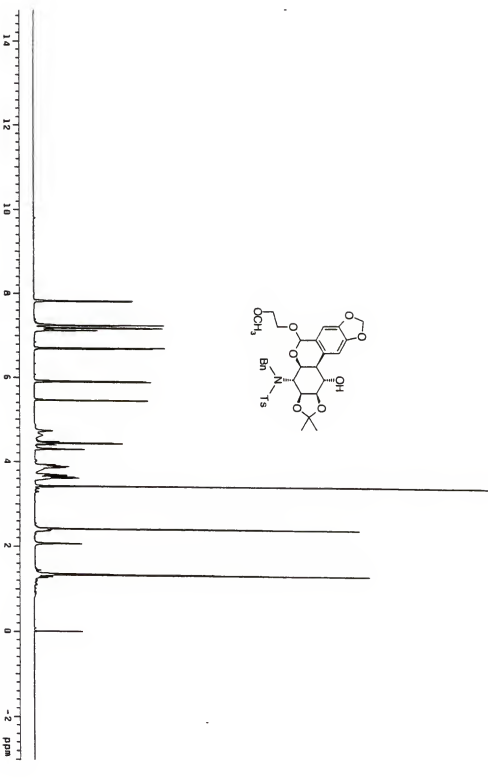
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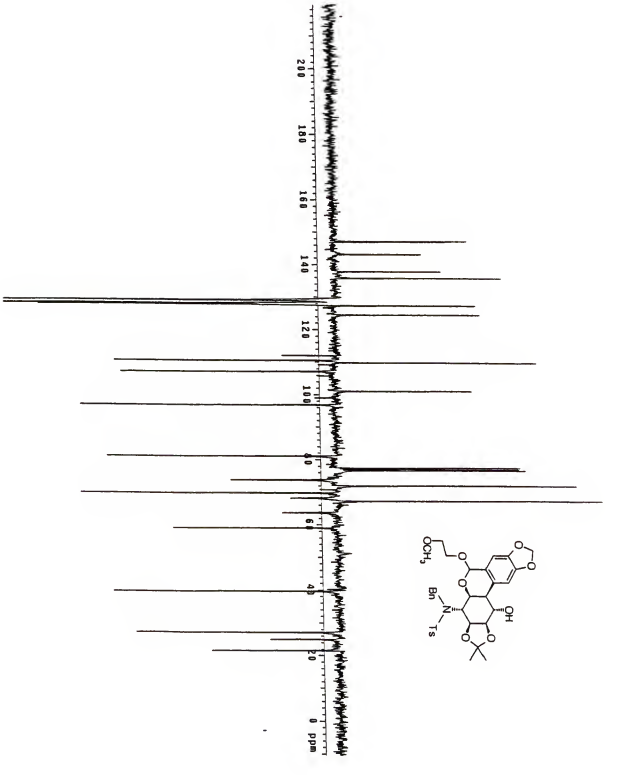
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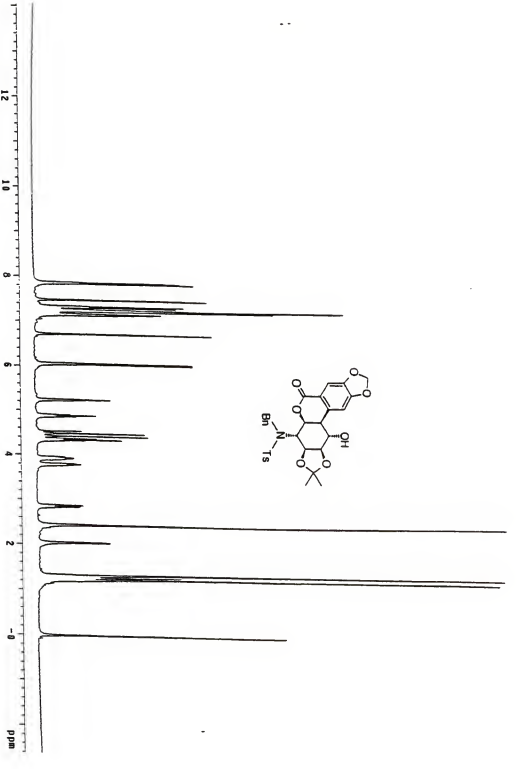
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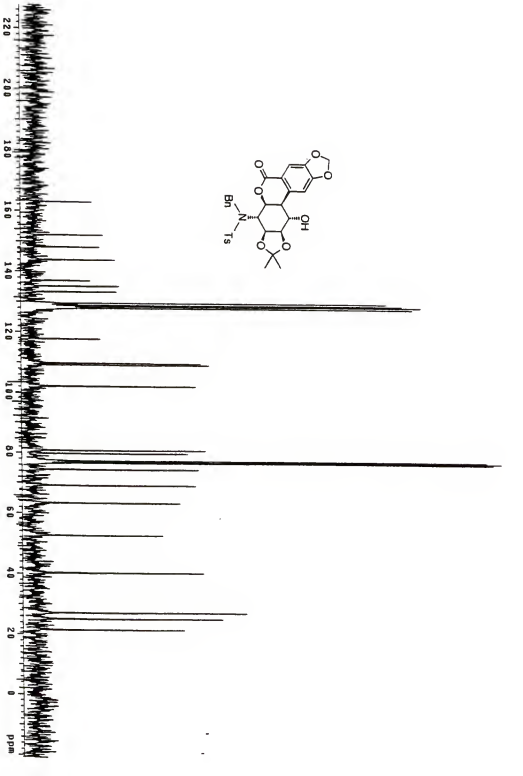
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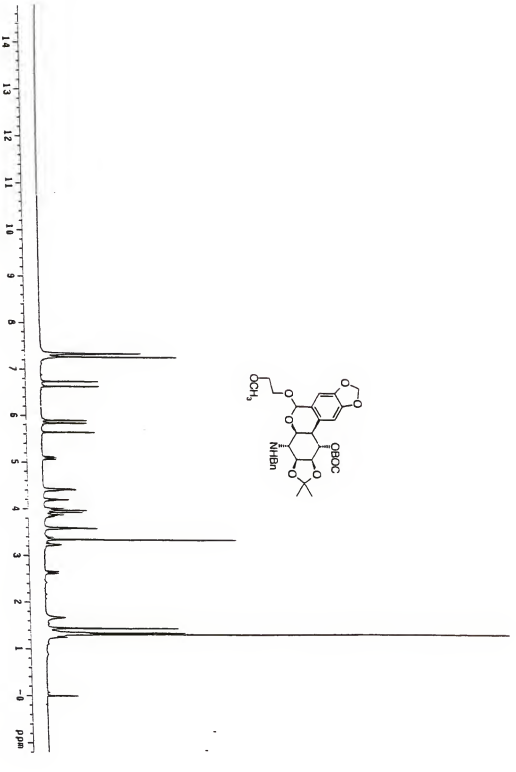
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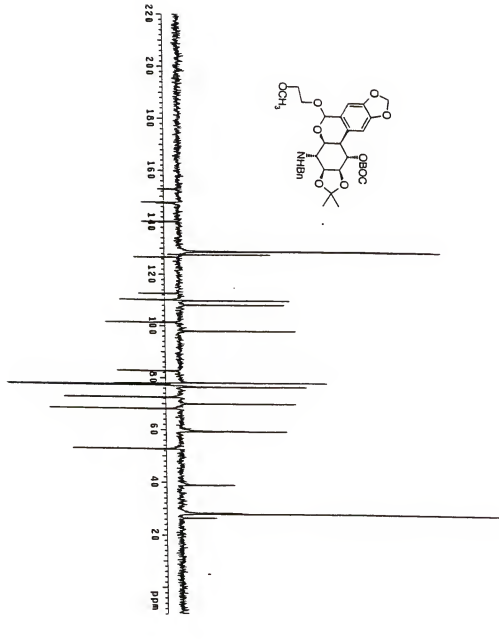
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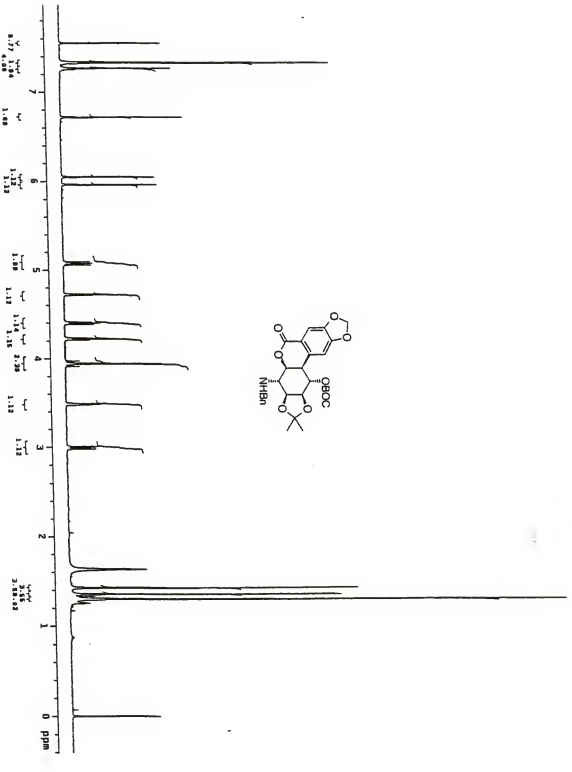
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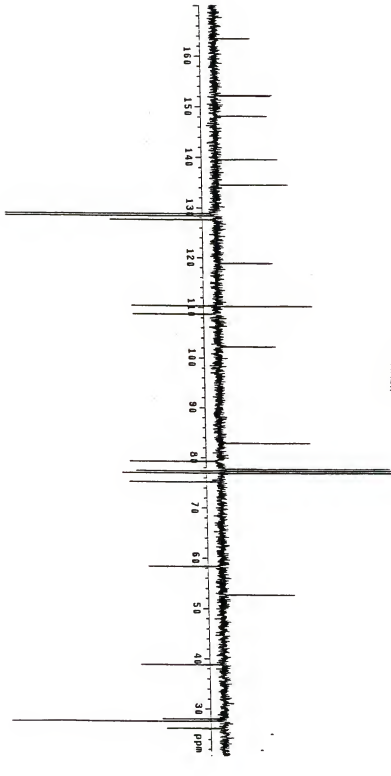
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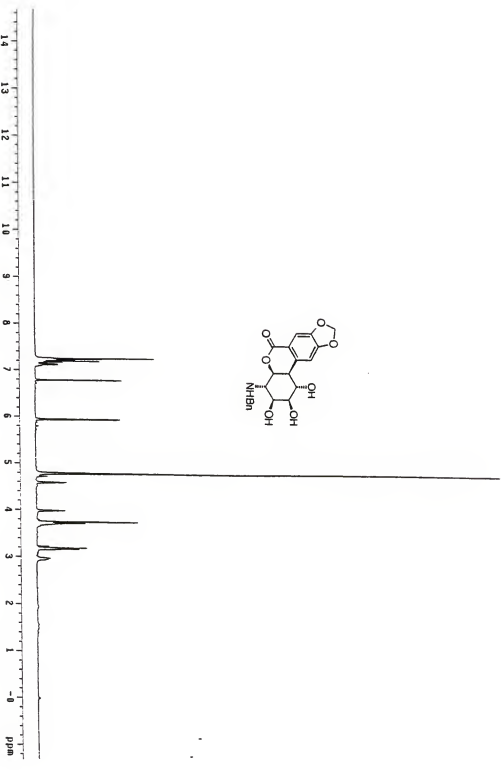
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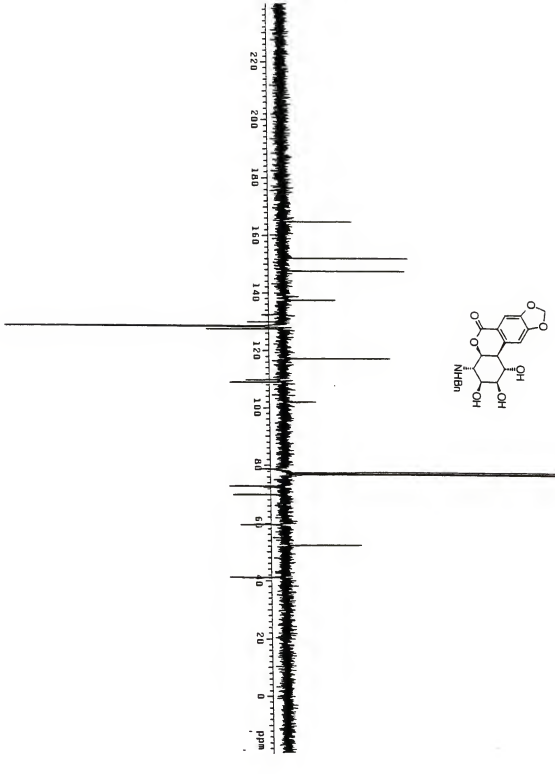
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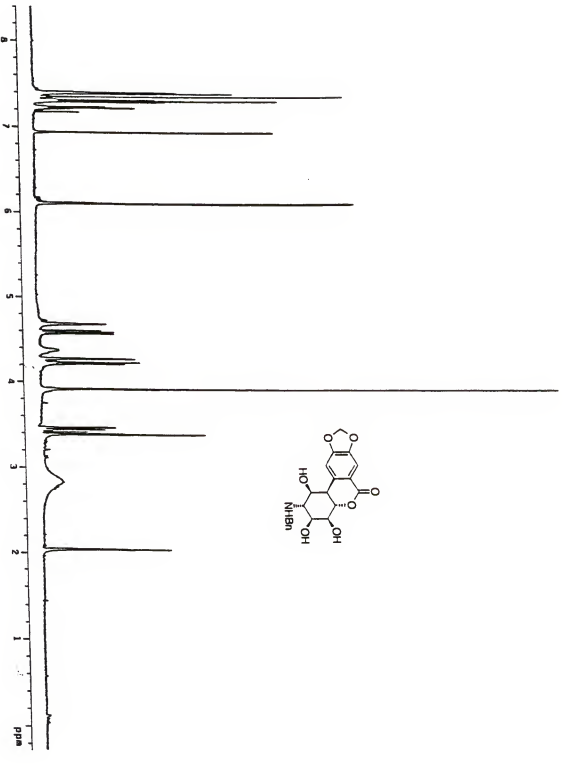
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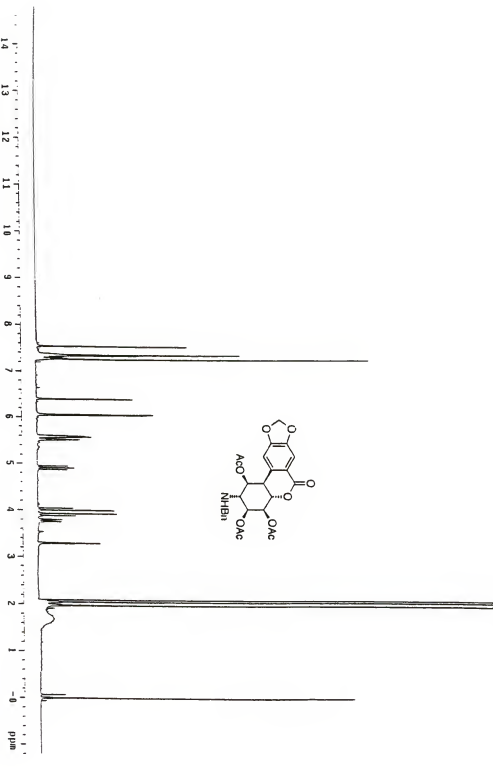
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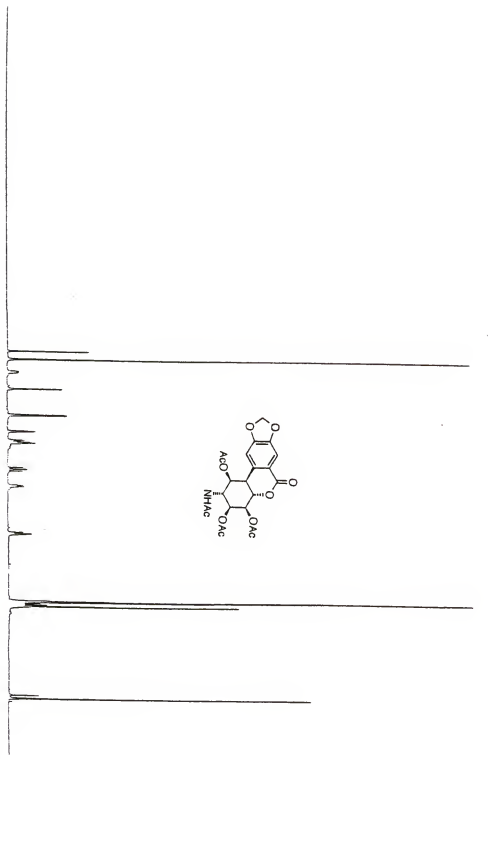
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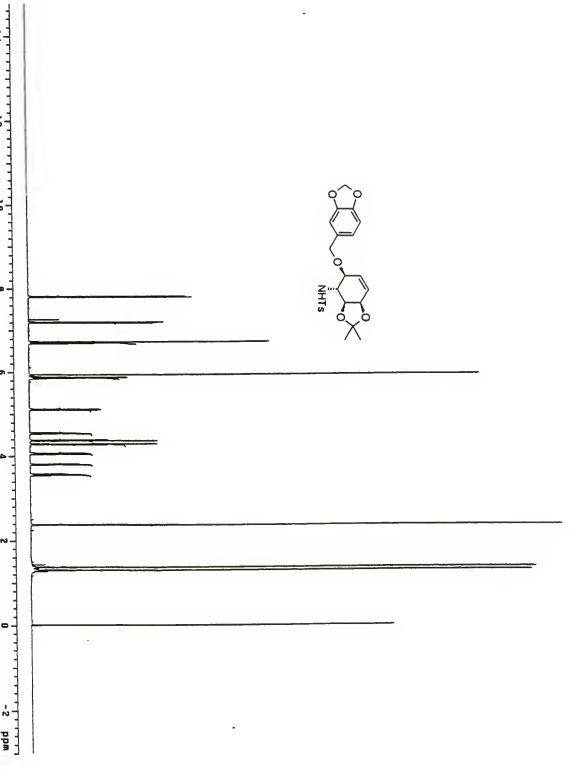
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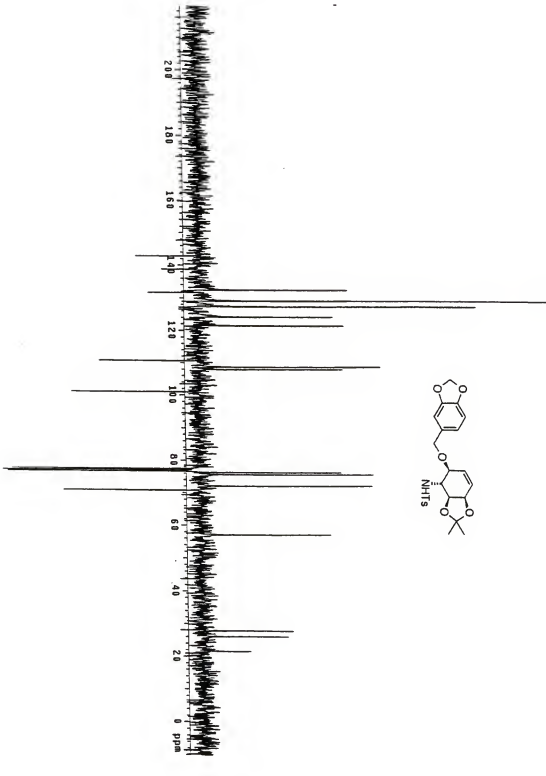
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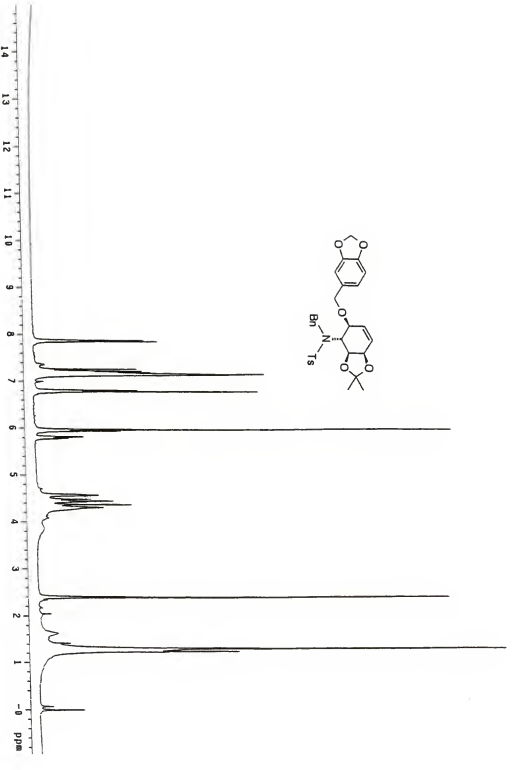
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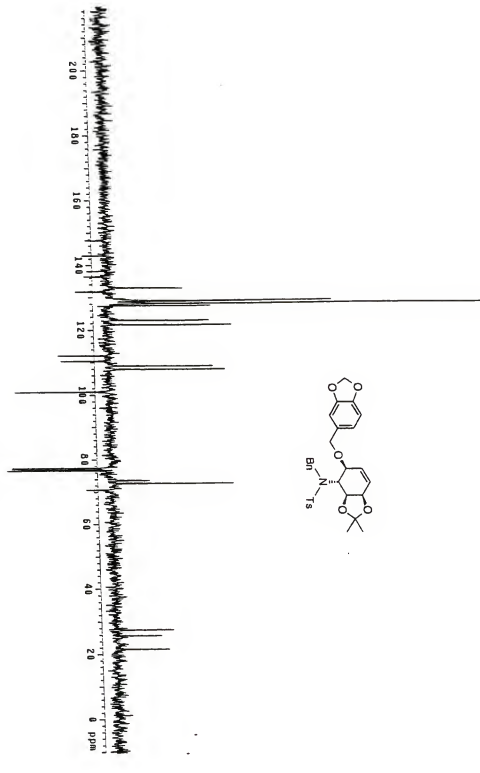
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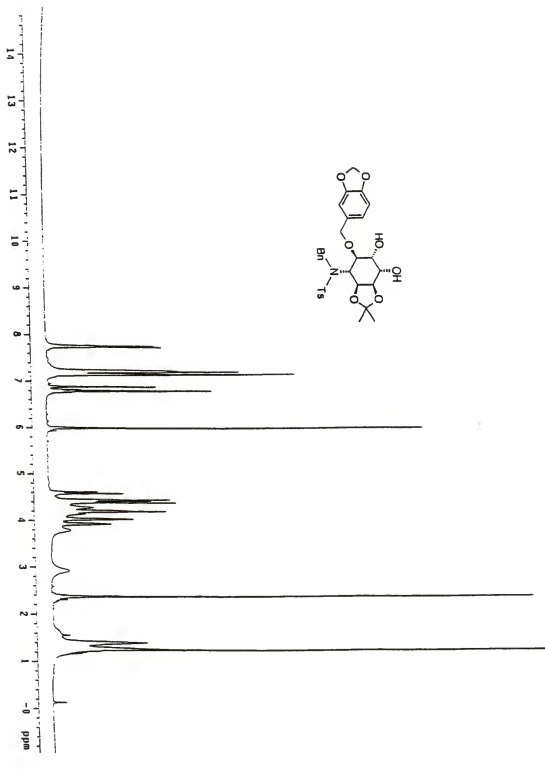
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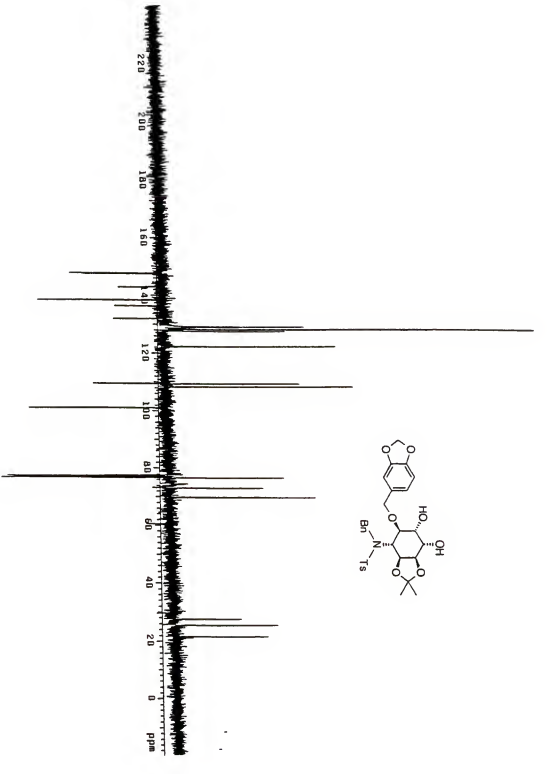
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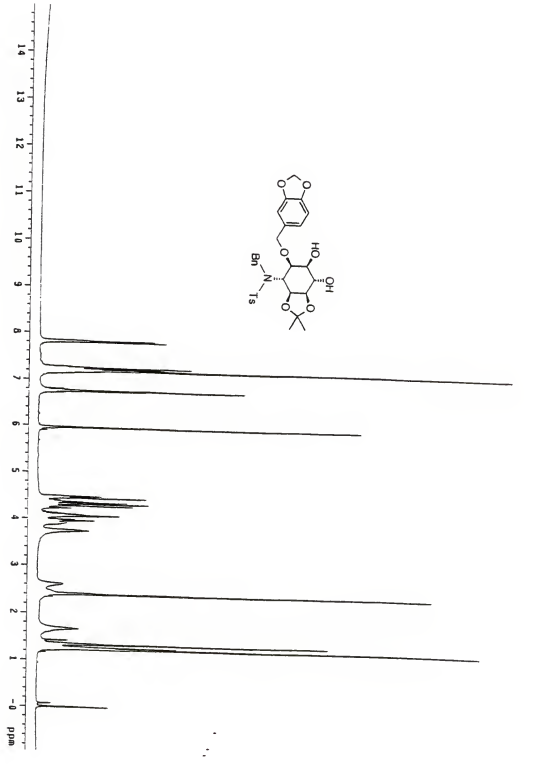
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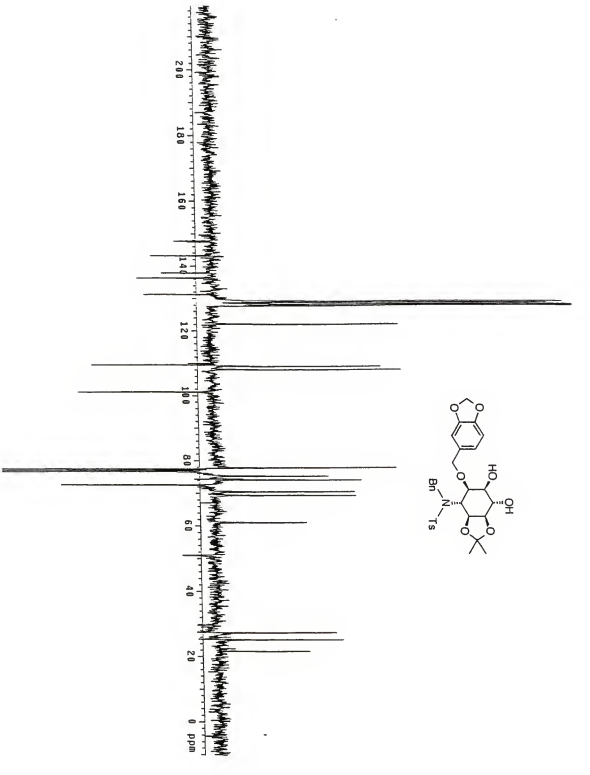
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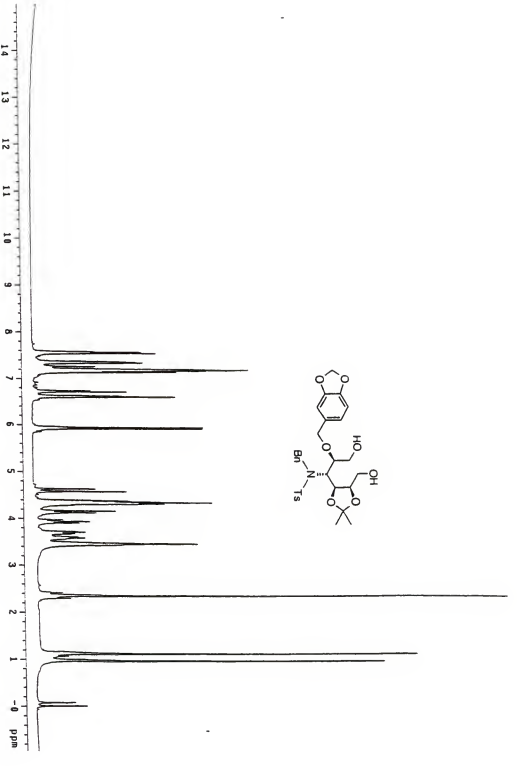
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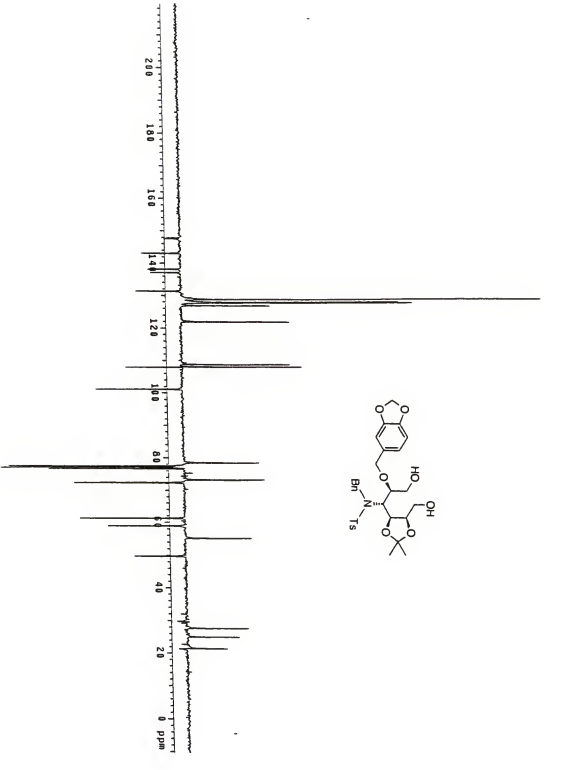
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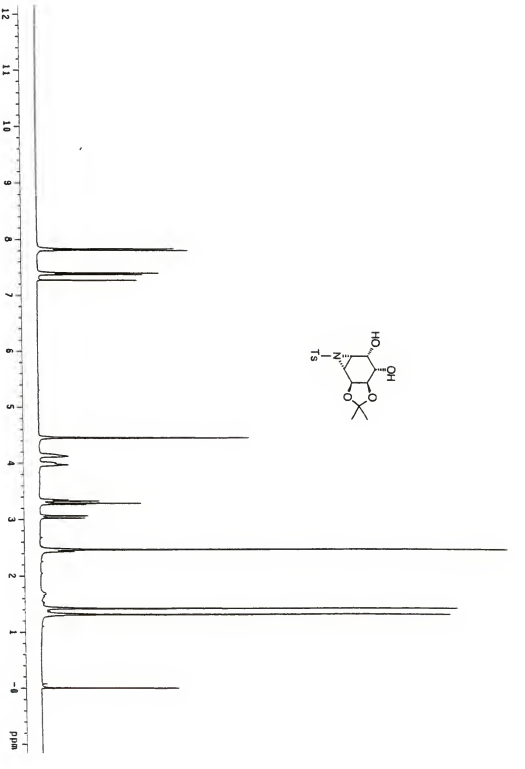
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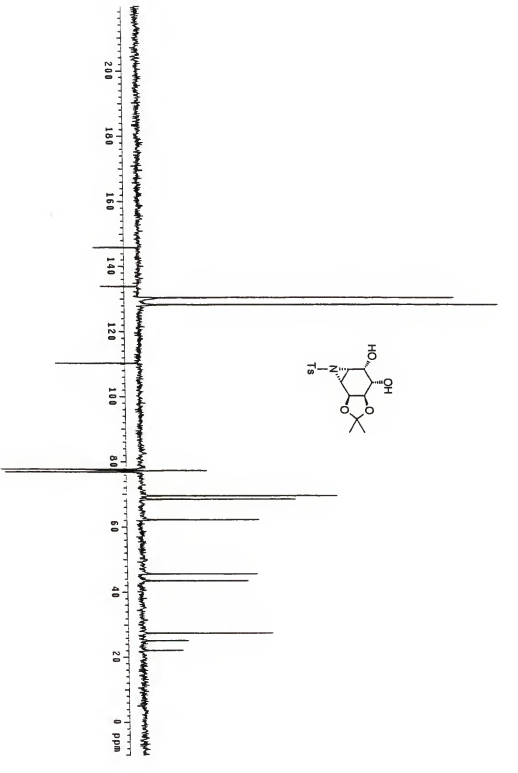
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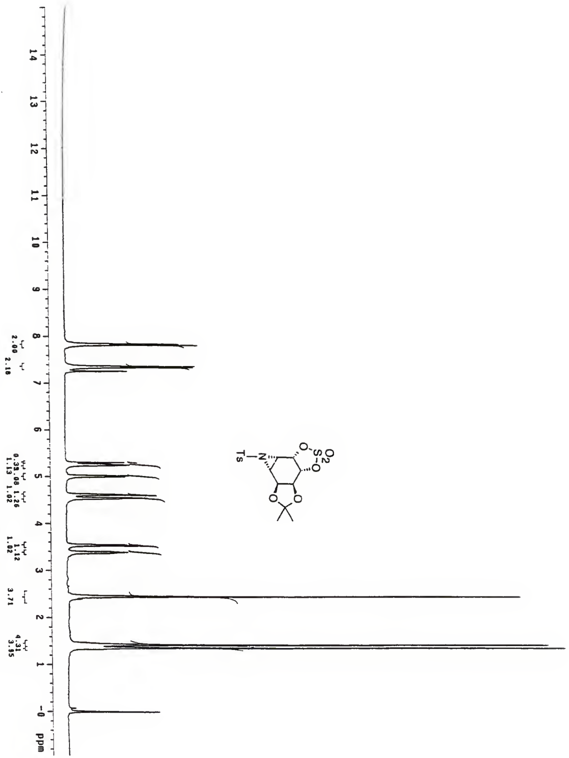
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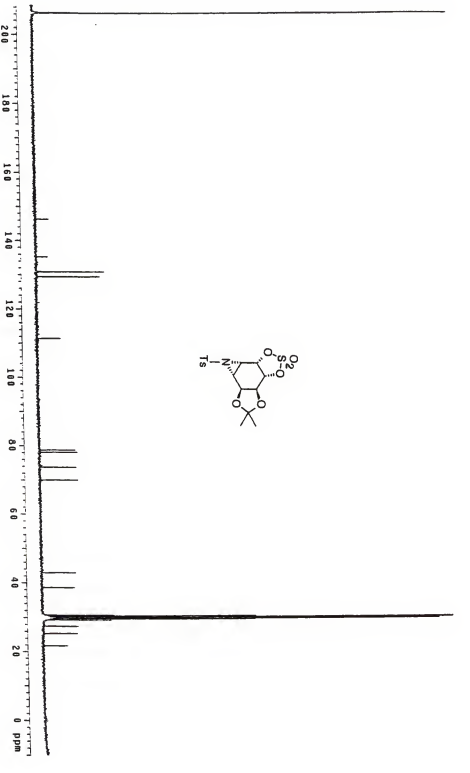
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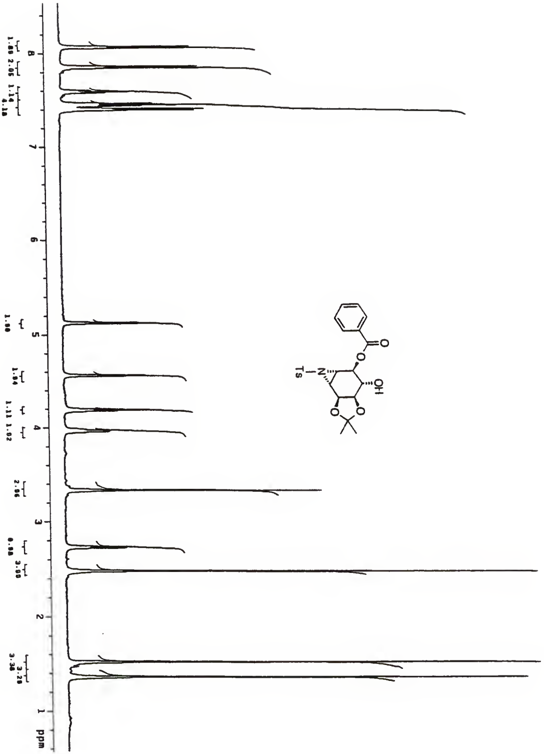
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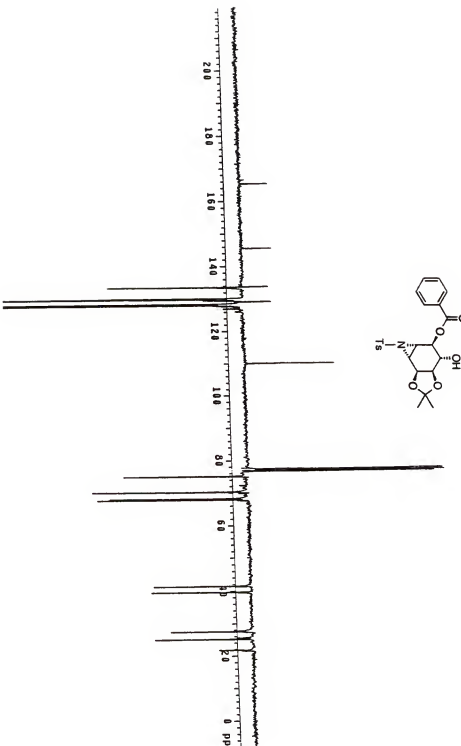
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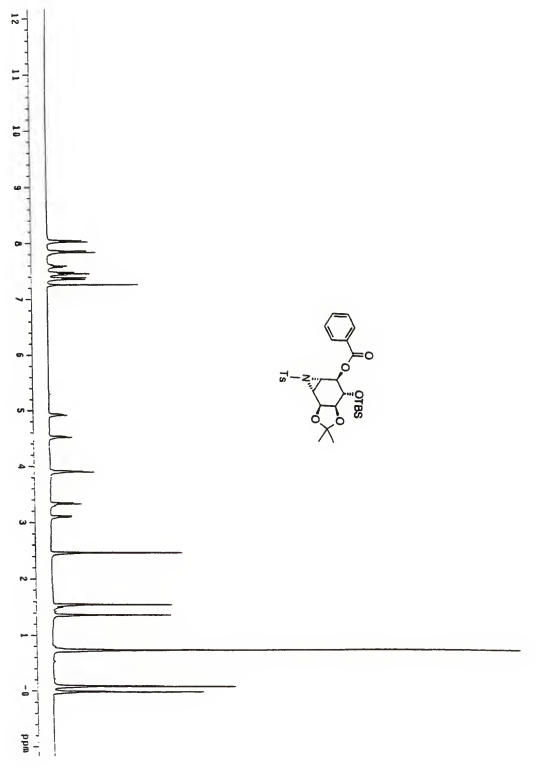
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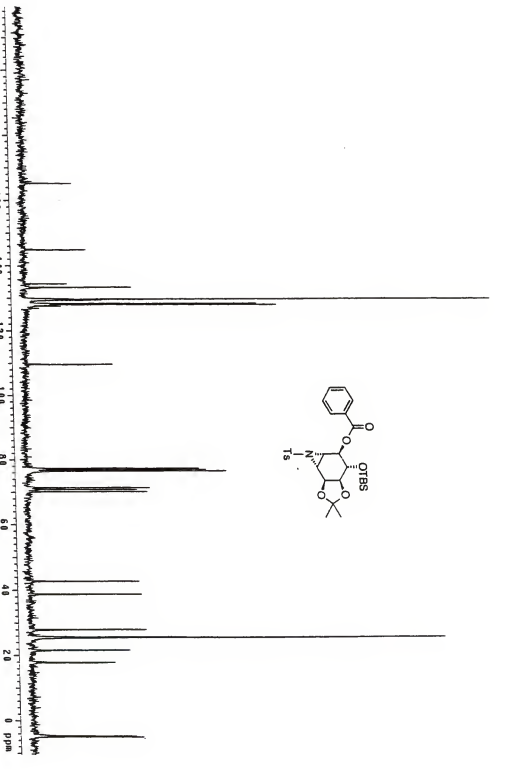
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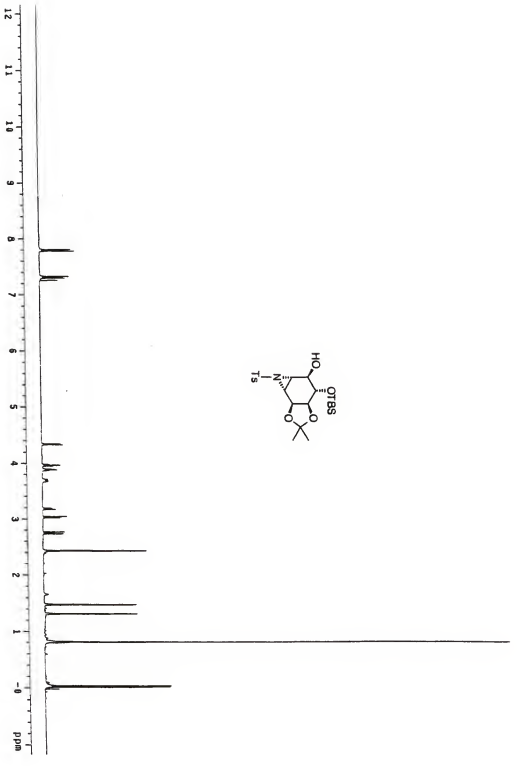
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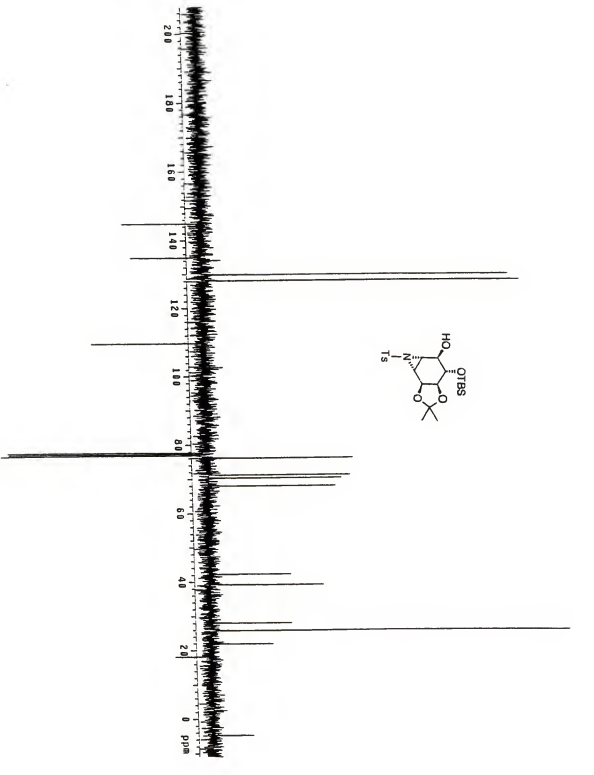
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BIOGRAPHICAL SKETCH

Stefan Schilling is the second of three brothers born to Peter and the late Inge Schilling in April of 1974 in Würzburg, Germany. After moving to the United States with his family, Stefan was raised in Charleston, South Carolina, where he lived for over 20 years.

Always wishing for the best, Stefan's parents emphasized the importance of a good education from an early age. Accordingly, Stefan's parents demanded academic excellence yet instilled a sense of humility with any accomplishments. After successfully completing grade school, Stefan attended Bishop England High School in Charleston, South Carolina, where he became interested in mathematics and in the sciences. Following completion of the high school curriculum, Stefan attended the College of Charleston that he majored in chemistry and graduated with honors. It was in the sophomore organic chemistry classes and in undergraduate research at the College of Charleston where Stefan began to take a keen interest in synthetic organic chemistry.

In August of 1996, Stefan committed to attend the graduate program in chemistry at the University of Florida and worked under the direction of Dr. Tomas Hudlicky. Research in addition to course work at the graduate level was very fascinating but often difficult. Stefan successfully passed his qualifying examination in August of 1999 and was admitted as a candidate in the doctoral program in chemistry. Currently, Stefan is working towards his Ph.D. in organic chemistry under the direction of his research advisor, Dr. Tomas Hudlicky. His research centers around strategies for the synthesis of (+)-7-deoxypancratistatin as well as structurally related analogs. Upon receiving his

Ph.D., Stefan plans to move to Raleigh, NC, where he plans to perform post-doctoral research at North Carolina State University under the supervision of Dr. Daniel Comins.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William Dolbier
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Vaneica Young
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth Sloan
Professor of Medicinal Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully acceptable, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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